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REACTIONS FROM DIPHTHERIA TOXOID

JACOB H. LANDES, M.D.
District Health Officer, Fort Greene and Bedford Districts
BROOKLYN

Since the introduction of fluid diphtheria toxoid and alum-precipitated toxoid for the immunization against diphtheria, both local and constitutional reactions following their use have been observed. There are many reports in the literature describing the types of reactions following the administration of alum-precipitated toxoid, but few reports have been published of reactions following the administration of fluid formaldehyde-treated toxoid. Difficulties are encountered in the recording of reactions following administration of toxoid. Observers do not agree on the definition of either local or constitutional reactions or on the degree of the severity of reactions. The number of reactions will naturally vary according to the interpretation. Some observers designate mere redness at the point of inoculation as a reaction. Others do not consider local reactions to be present unless the area of redness is extensive or there is pain interfering with the ordinary function of the arm. In many instances there is no adequate follow-up of children inoculated. In others, reactions are judged by a history obtained from the parent or child, and that would naturally vary with the person reporting.

In a series of 1,082 injections of alum-precipitated toxoid, Lewis [1] observed 35 mild and 8 severe reactions. According to his observation, 3 per cent of reactions were mild and fewer than 1 per cent could be classed as severe. Most of these reactions occurred in children over 8 years of age. The localized reactions consisted of extensive redness and swelling of the arm with pain and tenderness lasting for several weeks. The mild reactions were described by him as merely discomfort for a day or two following the injections.

Fulton and co-workers [2] reported local reactions in about half of the children who received from 0.1 to 0.3 cc. of alum-precipitated toxoid. In 1 child a sterile abscess developed. In one school these investigators observed that reactions following injection of 0.1 cc. of alum-precipitated toxoid occurred more often in children who gave negative Schick reactions than in children with positive Schick reactions. They maintained that the severity of reactions is determined more by the sensitivity of the child than by the size of the dose administered, although in a subsequent paper [3] they assumed that "the smaller the dose the less will be the degree of reaction."

Harrison [4] observed that the immediate local or general reactions following injections of precipitated toxoid were no more noticeable than those following injections of crude toxoid, although the injection of any insoluble precipitate will of itself set up some degree of local irritation. He also maintained that reactions frequently resulting in formation of abscesses are more common than the reports in the literature indicate.

1. Lewis, J. T.: M. Officer **62**:235-237 (Dec. 16) 1939.
2. Fulton, F., and others: Brit. M. J. **1**:315-320 (March 7) 1942.
3. Fulton, F., and others: Brit. M. J. **1**:349-352 (March 14) 1942.
4. Harrison, W. T.: Am. J. Pub. Health **25**:298-300 (March) 1935.

Monroe and Volk [5] studied the incidence of reactions from diphtheria toxoid and from alum-precipitated toxoid. They reported approximately 4 per cent of local and general reactions from toxoid without alum and a slightly higher percentage of reactions from alum-precipitated toxoid.

McGinnes, Stebbins and Hart [6] in a study of a series of 353 children inoculated with alum-precipitated toxoid observed that 19 per cent of them showed moderate or severe local and systemic reactions. In a parallel series of observations on two groups of children, one of which received alum-precipitated toxoid and the other untreated toxoid, the authors observed a similarity of the local and systemic reactions in the two groups. They concluded that there was no evidence that the reactions caused by alum-precipitated toxoid are in any way different from those elicited by untreated toxoid.

In a study recently conducted by Volk and Bunney,[7] these investigators found a higher percentage of local reactions following use of alum-precipitated toxoid than from fluid toxoid. Interestingly, local reactions, moderate and severe, following administration of 0.5 cc. of alum-precipitated toxoid and fluid toxoid to different groups of children were more numerous than reactions following 0.1 cc. of toxoid.

About two years ago, of a series of over 11,000 school children who were inoculated with plain toxoid, I [8] reported less than 0.3 per cent in whom reactions developed necessitating a visit by a physician. It was further observed that reactions in school children occurred more frequently in those 9 years of age or over than in younger school children.

This paper discusses the frequency of local and constitutional reactions following inoculations of formaldehyde-treated toxoid in a group of 7,794 school children from 5 through 10 years of age. During the months of May and June 1942 the Department of Health of the city of New York conducted an intensive campaign of immunization of school children under 11 years of age against diphtheria. The department advocated a full course of injections for all children who had never received any protection against diphtheria and advised a "booster dose," or supplementary inoculation, of 0.1 to 0.2 cc. of diphtheria toxoid for all school children under 10 years of age who had been immunized [9] three or more years before. This report is based on the work performed in the Fort Greene and Bedford districts in the borough of Brooklyn.

Immunizations against diphtheria were performed in more than sixty public and parochial schools of those districts by a staff of six school physicians. The physicians and nurses were instructed to report any reactions that they observed and also to investigate reports of children who had some form of discomfort, such as extensive redness, pain, interference with function or rise in temperature. On inoculation each child received a mimeographed notice addressed to the mother advising her not to become alarmed if a slight redness or swelling developed following the injection. She was also advised to apply a boric acid dressing to the site of inoculation if redness or swelling did develop.

During these two months, 7,794 injections of diphtheria toxoid were administered. Of these, 6,223 were supplementary doses of 0.1 to 0.2 cc. administered

5. Monroe, J. D., and Volk, V. K.: Am. J. Pub. Health **24**:342-348 (April) 1934.

6. McGinnes, G. F.; Stebbins, E. L., and Hart, C. D.: Am. J. Pub. Health **24**:1141-1147 (Nov.) 1934.

7. Volk, V. K., and Bunney, W. E.: Am. J. Pub. Health **32**:700-708 (July) 1942.

8. Landes, J. H.: New York State J. Med. **40**:1594-1598 (Nov. 1) 1940.

9. In this paper the term "immunized children" refers to children who received a series of injections against diphtheria. Routine Schick tests were not performed, and the immunization status is actually not known.

to children under 11 years of age who gave a history of previous immunization. One thousand, five hundred and seventy-one children gave no history of previous immunization, and they received the first dose of 0.25 cc. of undiluted toxoid, the dose thus not differing greatly from that administered to the first group of children. Three fourths of the children, or 5,843, were white, and the remainder, 1,951, were Negro.

While the school nurses did not do routine follow-up on every child inoculated, they were on the alert to discover children who showed either local or systemic reactions. Teachers were asked in most instances to refer to the nurses all children who gave a history of sore arms or other discomfort. The teachers were also to refer to the nurses children who had been absent because of a reaction to the inoculation. It must, of course, be realized that children might have had reactions without informing the nurse or teacher. It is also true that the notice sent home to the parents eliminated, beyond doubt, a number of children with ordinary sore arms of whom the nurses were unaware.

TABLE 1.—*Reactions From Diphtheria Toxoid in Previously Immunized and Unimmunized School Children 5 Through 10 Years of Age*

	Number Inoculated	Number of Reactions
Previously immunized	6,223	10
Unimmunized	1,571	2
Total	7,794	12

TABLE 2.—*Reactions From Diphtheria Toxoid in White and Negro School Children 5 Through 10 Years of Age*

	Number Inoculated	Number of Reactions
White children	5,843	9
Negro children	1,951	3
Total	7,794	12

Of the entire group of children inoculated, 12 were referred to the nurse as having had reactions, either local or systemic or both. Ten reactions occurred among previously immunized children, and 2 reactions occurred in children who were never before inoculated (table 1). In 7 instances, the nurses deemed those reactions to be of such severity as to necessitate a home visit by a physician. Of the other 5 children, 1 was treated by the family physician and 4 were referred to the school physicians for consultation during their regular school visits.

Of the 12 children who presented evidences of a reaction, 9 were white and 3 were Negro (table 2). The white children had received merely a supplementary inoculation. Of the Negro children, 1, a 9 year old child, showed a reaction following a supplementary inoculation, and 2 children, 7 and 8 years old, who had never been immunized previously, also showed a reaction. The proportion of reactors among the white and the Negro children was thus about the same. Among the 949 white children who were previously unimmunized and who therefore received the first injection of the series, there were no reactions reported. Here the observation of Fulton [3] may be recalled, that reactions occurred more often in children who gave negative Schick reactions than in those who had positive Schick reactions.

Of the 12 children referred to, all had pronounced redness and swelling of the arm. One 9 year old child acquired an edema of the hand and of both ankles on the third day after the injection. The edema disappeared within forty-eight hours. The child was away from school for three days. Three children had a rise in temperature, 1 as high as 103.5 F.; the latter was absent from school for three days. All of those children had received a supplementary inoculation. The majority of the 12 children were away from school two to four days following the injection. Absence, however, is no criterion of the extent of the reaction, as some children might have stayed away for reasons other than local or systemic effects due to the inoculation.

Analysis of the incidence of reactions in the various age groups from 5 through 10 years reveals no significant difference in the number of reactions in any group (table 3). In my previous study,[8] it was shown that when 1 cc. of fluid toxoid was administered to previously immunized children the frequency of reactions was much greater in children 9 years of age and older than in younger school children.

In this connection I have compared the effect of dosage of fluid toxoid on the number of reactions in previously immunized children. When 1 cc. of toxoid was administered, the incidence of reported reactions was less than 0.3 per cent. In

TABLE 3.—*Reactions Following Administration of 0.2 Cc. of Fluid Toxoid to Previously Immunized White and Negro School Children 5 Through 10 Years of Age*

Age Group	Number of Children	Number of Reactions	Per Cent of Reactions
5	87	0	0
6	1,048	0	0
7	930	2	0.21
8	1,413	4	0.28
9	2,030	3	0.15
10	715	1	0.14
Total	6,223	10	0.16

this series, including an almost similar number of previously immunized children, there were only 10 reported reactions of moderate or severe intensity, or less than 0.2 per cent. The difference in the number of reported reactions in the two groups is of no statistical significance.

SUMMARY

An analysis is presented of the incidence of reactions from fluid toxoid among 7,794 white and Negro children from 5 through 10 years of age attending public schools in the Fort Greene and Bedford districts in Brooklyn.

Ten out of 12 reported reactions occurred in previously immunized school children.

There were no reported reactions following the first dose of 0.25 cc. of fluid toxoid in 949 unimmunized white school children.

There was no difference in the frequency of reactions between white and Negro children.

There was no difference in the frequency of reactions among the various age groups.

Though the number of reactions in previously immunized children following injection of 0.1 to 0.2 cc. of fluid toxoid was fewer than those found in a previous study, when 1 cc. of fluid toxoid was administered to a similar group of children, this difference is of no statistical significance.

295 Flatbush Avenue Extension.

CAUSES OF PREMATURITY

III. INFLUENCE OF RACE AND SEX ON DURATION OF GESTATION AND WEIGHT AT BIRTH

NINA A. ANDERSON, M.D.
PHILADELPHIA
AND
ESTELLE W. BROWN, B.S.
AND
R. A. LYON, M.D.
CINCINNATI

The influence of race and sex on the incidence of prematurity has been considered in several previous investigations. Riggs [1] and Pride [2] found that the average birth weight of Negro infants is less than that of white infants. Employing birth weight as the criterion for prematurity, Woodbury,[3] Ford [4] and Bivings [5] noted a higher incidence of prematurity in the Negro race. It has long been known that the average birth weight of girls is less than that of boys. The influence of both race and sex on birth weight has been reported by Bakwin and Bakwin [6] and by Dunham, Jenss and Christie.[7] In a roentgenographic study of the osseous development of newborn infants, Christie, Dunham, Jenss and Dippel [8] have shown that for the same weight groups the center of ossification for the cuboid bone is more frequently present in infants of the Negro race than of the white race and in female infants than in male infants. Duffield, Parker and Baumgartner [9] noted the influence of race and sex on the birth weights of the infants in a large series of cases which they analyzed in relation to neonatal mortality.

From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati, College of Medicine.

1. Riggs, T. F.: Comparative Study of White and Negro Pelves with a Consideration of the Size of the Child and Its Relation to Presentation and Character of Labor in the Two Races, Bull. Johns Hopkins Hosp. **12**:42, 1904.

2. Pride, W. T.: Pelvic Measurements in White and Colored Female and Their Significance in Child Birth: Study of One Thousand Four Hundred Cases, Am. J. Obst. & Gynec. **31**:495-501 (March) 1936.

3. Woodbury, R. M.: Causal Factors in Infant Mortality, Publication 142, United States Department of Labor, Children's Bureau, 1925.

4. Ford, H. W.: Statistical Study on Neonatal Mortality with Special Relation to the Factor of Mother Nativity, Am. J. Hyg. **7**:89-104 (Jan.) 1927.

5. Bivings, L.: Racial, Geographic, Annual and Seasonal Variations in Birth Weights, Am. J. Obst. & Gynec. **27**:725-728 (May) 1934.

6. Bakwin, H., and Bakwin, R. M.: Body Build in Infants: Anthropometry in the New-Born, Human Biol. **6**:612-626 (Dec.) 1934.

7. Dunham, E. C.; Jenss, R. M., and Christie, A. U.: Consideration of Race and Sex in Relation to the Growth and Development of Infants, J. Pediat. **14**:156-160 (Feb.) 1939.

8. Christie, A. U.; Dunham, E. C.; Jenss, R. M., and Dippel, A. L.: Development of Center for Cuboid Bone in New-Born Infants: Roentgenographic Study, Am. J. Dis. Child. **61**:471-482 (March) 1941.

9. Duffield, T. J.; Parker, S. L., and Baumgartner, L.: Birth Weight and Its Relation to Neonatal Mortality: Analysis of Data on Live Births in New York City in 1939, Child **5**:123-129 (Nov.-Dec.) 1940.

Less attention has been paid to the differences between the gestation periods of the Negro and the white race. Hotelling and Hotelling [10a] and Meyer [10b] have reported shorter gestation periods among Negro women than among white women. In many of these studies, the number of Negro patients was considerably smaller than the number of white patients. In our series of patients, about 60 per cent were white and 40 per cent Negro.

Our studies demonstrate that race and sex influence birth weight and that race influences gestation period.

OBSERVATIONS

This study includes records of 5,686 consecutive live-born infants not the result of multiple pregnancy born in the obstetric wards of the Cincinnati General Hospital from July 1938 to January 1941. Any infant who showed after birth either heart beat or movement of respiratory or voluntary muscles was considered live born,

TABLE 1.—*Frequency Distribution by Weight of Single Live-Born White and Negro Infants*

Birth Weight					White		Negro		
Lb.	Oz.		Lb.	Oz.	Male	Female	Male	Female	Total
1	0	to	1	7	..	1	..	2	3
1	8	to	1	15	3	3	1	3	10
2	0	to	2	7	6	4	4	3	17
2	8	to	2	15	5	1	3	1	10
3	0	to	3	7	7	7	4	11	29
3	8	to	3	15	8	4	5	13	30
4	0	to	4	7	12	16	15	18	61
4	8	to	4	15	29	26	28	27	110
5	0	to	5	7	52	61	54	65	232
5	8	to	5	15	78	104	86	107	375
6	0	to	6	7	152	220	166	197	735
6	8	to	6	15	238	283	193	238	952
7	0	to	7	7	311	320	236	208	1,075
7	8	to	7	15	303	250	171	133	857
8	0	to	8	7	236	173	84	67	560
8	8	to	8	15	143	111	50	36	340
9	0	to	9	7	75	42	27	16	160
9	8	to	9	15	42	17	11	5	75
10	0	to	10	7	21	10	4	2	37
10	8	to	10	15	3	3	1	1	8
11	0	to	11	7	2	2	1	..	5
11	8	to	11	15	3	..	..	..	3
12	0	to	12	7	..	..	..	..	..
12	8	to	12	15	2	..	..	..	2
Grand total.....					1,731	1,658	1,144	1,153	5,686
Total by race.....					3,389		2,297		

regardless of presumed viability. Because of the distribution of the white and Negro populations in a group of approximately the same economic status and because Cincinnati does not provide facilities for home deliveries, this appeared to be a satisfactory sample for study. Position in the family and maternal age have been considered factors which may influence birth weight. The white and Negro populations are satisfactory for comparison from the point of view of gravidity. The mean age of the mothers of the white infants was about 24½ years. The Negro mothers were almost a year younger. This difference is almost entirely accounted for by the fact that the Negro mothers were younger at the time of their first pregnancy, since the interval between pregnancies was almost the same for the two races. The mean age at first pregnancy was 20 years for the white and 19.2 years for the Negro mothers. The scope of the study did not permit us to

10. (*a*) Hotelling, H., and Hotelling, F.: New Analysis of Duration of Pregnancy Data. Am. J. Obst. & Gynec. **23**:643-657 (May) 1932. (*b*) Meyer, A. W.: Fields, Graphs and Other Data on Fetal Growth, Contrib. Embryol. **2**:55-68, 1915; cited by Hotelling and Hotelling.[10a]

make any attempt to evaluate the nutritional status of the mothers. The average nongravid weight of the white mothers was slightly less than that of the Negro mothers. The effect of birth order and maternal age on birth weight will be studied in detail later as data on women who repeatedly enter the wards for the births of their children are assembled.

The frequency distribution by birth weight of these 5,686 infants is shown in table 1 and is graphically represented in percentages and cumulative percentages in charts 1 and 2. In chart 1 the mean birth weight for each sex and race is indicated in white. The mean birth weights for each race and sex with their standard deviations are shown in table 2. The difference in birth weight observed between male and female infants of the same race is about 4 ounces (115 Gm.) and that between white and Negro infants of the same sex is about 7 ounces (195 Gm.). These differences, together with the value of "t," by which their significance was tested, are also given in table 2. The test applied is the "t" test of "Student," in which "t" is the difference between two means divided by the standard error of the difference and "P" is the probability that a difference as large as or larger than that observed would arise by chance alone. For a series as large as this, in

TABLE 2.—*Mean Birth Weights of Single Live-Born White and Negro Infants*

	Number of Cases	Means and Standard Deviations							
		Lb.	Oz.		Lb.	Oz.	Gm.		
White males	1,731	7	6	±	1	5	3,349	±	594
White females	1,658	7	2	±	1	3	3,234	±	541
Negro males	1,144	6	15	±	1	3	3,154	±	541
Negro females	1,153	6	11	±	1	3	3,053	±	539

Significance of Differences in Birth Weights

	Number of Cases	Differences		"t"	"P"
		Oz.	Gm.		
White: males and females	3,389	4	115	5.9253	<0.001
Males: white and Negro	2,875	7	195	8.9205	<0.001
Negro: males and females	2,297	4	111	5.0841	<0.001
Females: white and Negro	2,811	7	191	9.1847	<0.001

which "n" may be considered infinity, a value of "t" of 1.960 corresponds to a value of "P" of 0.05. This indicates that a difference as large as or larger than that observed would arise by chance alone in only 5 per cent of similar trials. As "t" becomes larger, "P" becomes smaller and the differences are of greater significance. A value of "P" of 0.05 or less is commonly accepted by statisticians as indicating a significant difference. It may be observed from table 2 that in every case "t" is considerably larger than the borderline value of 1.960 and "P" is correspondingly small, which indicates a high degree of significance for the race and sex differences in birth weight.

We have recorded the gestation period, as estimated from the first day of the last menstrual period, for 4,843 of the 5,686 infants. There were 797 mothers for whom the date of the last menstrual period could not be established, 45 mothers who did not menstruate between pregnancies and 1 girl who became pregnant before the menstrual cycle was established. The distribution of these gestation periods is given in table 3. The means and standard deviations are recorded in table 4. When the "t" test is applied, it is observed that the difference between the gestation periods for male and female infants of the same race is not significant but that the five and one-half days difference in gestation between white and Negro infants is a highly significant figure. Since there is no significant sex difference in gestation period, male and female infants of the same race have been considered

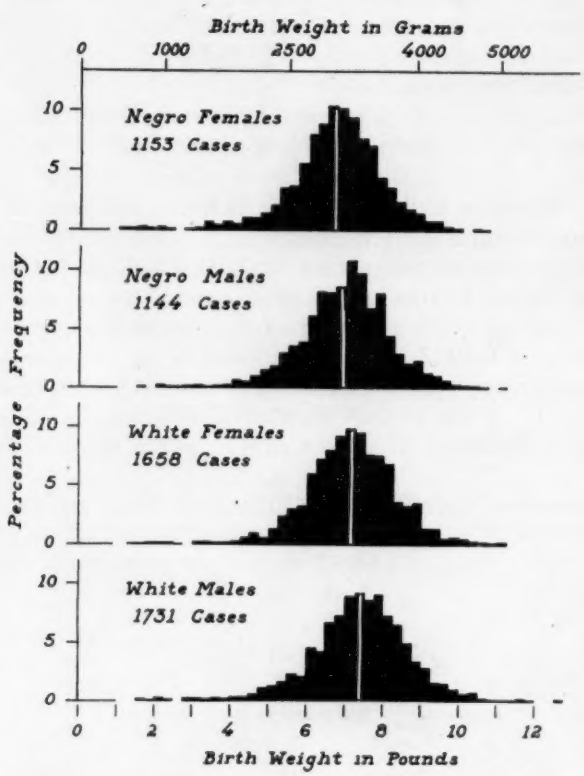

Fig. 1.—Frequency distribution of birth weights of 5,686 infants.

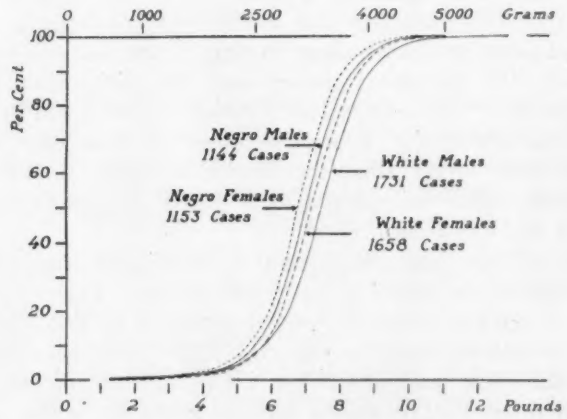

Fig. 2.—Cumulative percentage frequencies of birth weights of white and Negro infants.

TABLE 3.—*Frequency Distribution by Gestation Period of Single Live-Born White and Negro Infants*

Gestation Period, Days	White			Negro		
	Male	Female	Total	Male	Female	Total
Less than 147	..	1	1	1	1	2
147-153	1	..	1	..	..	..
154-160	1	1	2	..	1	1
161-167	1	1	2	1	1	2
168-174	3	3	6	2	..	2
175-181	2	2	4	1	2	3
182-188	2	1	3	..	1	1
189-195	5	1	6	1	4	5
196-202	3	1	4	2	3	5
203-209	7	2	9	1	8	9
210-216	5	1	6	3	4	7
217-223	10	6	16	3	9	12
224-230	10	3	13	8	10	18
231-237	8	20	28	23	13	36
238-244	31	26	57	33	27	60
245-251	38	29	67	30	38	68
252-258	43	51	94	46	42	88
259-265	91	60	151	72	64	136
266-272	150	152	302	140	133	273
273-279	265	251	516	182	219	401
280-286	359	358	717	173	184	357
287-293	238	247	485	111	103	214
294-300	108	117	220	54	40	94
301-307	52	55	107	27	29	56
308-314	32	18	50	11	9	20
315-321	23	12	35	6	5	11
322-328	14	9	23	5	3	8
329-335	2	1	3	1	..	1
336-342	4	5	9	1	..	1
343-349	1	3	4	1	..	1
350 and more	5	2	7	1	2	3
Total known	1,509	1,439	2,948	940	955	1,895
Unknown	211	205	416	194	187	381
No menstrual period	11	14	25	10	11	21
Grand total	1,731	1,658	3,389	1,144	1,153	2,297

TABLE 4.—*Gestation Periods of Single Live-Born White and Negro Infants as Estimated from the First Day of Last Menstrual Period*

	Means and Standard Deviations, Days							
	Last Menstrual Period Known		Gestation Period, 210 Days or More		Birth Weight, 5 Lb. 8 Oz. or More		Birth Weight, 5 Lb. 8 Oz. or More and Gestation, 238 Days or More	
	No.	Mean ± S. D.	No.	Mean ± S. D.	No.	Mean ± S. D.	No.	Mean ± S. D.
White males	1,509	279.0 ± 21.7	1,484	280.5 ± 18.3	1,407	281.3 ± 18.4	1,380	282.6 ± 15.8
White females	1,439	279.9 ± 19.5	1,426	280.8 ± 17.0	1,334	282.3 ± 15.8	1,321	282.8 ± 14.9
Negro males	940	274.7 ± 20.6	931	275.6 ± 18.4	852	277.1 ± 17.2	835	278.1 ± 14.2
Negro females	955	273.3 ± 21.6	934	275.1 ± 17.9	840	276.7 ± 17.3	818	278.2 ± 16.6
White males and females	2,948	279.5 ± 20.7	2,910	280.7 ± 17.7	2,741	281.8 ± 17.2	2,701	282.7 ± 15.4
Negro males and females	1,895	274.0 ± 21.1	1,865	275.3 ± 18.1	1,692	276.9 ± 17.3	1,653	278.2 ± 15.2

	Significance of Differences Between Means											
	Diff., Days	"t"	"P"	Diff., Days	"t"	"P"	Diff., Days	"t"	"P"	Diff., Days	"t"	"P"
White males and females	0.9	1.1875	0.3-0.2	0.3	0.4746	0.7-0.6	1.0	1.5254	0.2-0.1	0.2	0.3635	0.7-0.6
Negro males and females	1.4	1.4348	0.2-0.1	0.5	0.5586	0.6-0.5	0.4	0.4861	0.7-0.6	0.1	0.1594	0.9-0.8
White and Negro	5.5	8.9348	<0.001	5.4	10.0896	<0.001	4.9	9.1797	<0.001	4.5	9.5482	<0.001

together. The frequency distributions expressed as percentages and cumulative percentages are shown in charts 3 and 4. In chart 3 the mean gestation period is indicated in white.

In order to be sure that the results observed were not influenced by the inclusion of an undue number of extremely small and extremely immature infants, these same calculations were carried out for three other groups. The first group contained

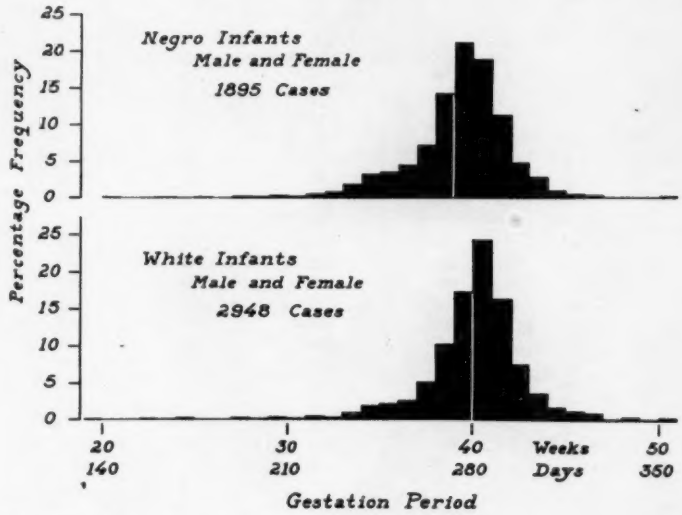

Fig. 3.—Frequency distribution of gestation periods of 4,843 infants.

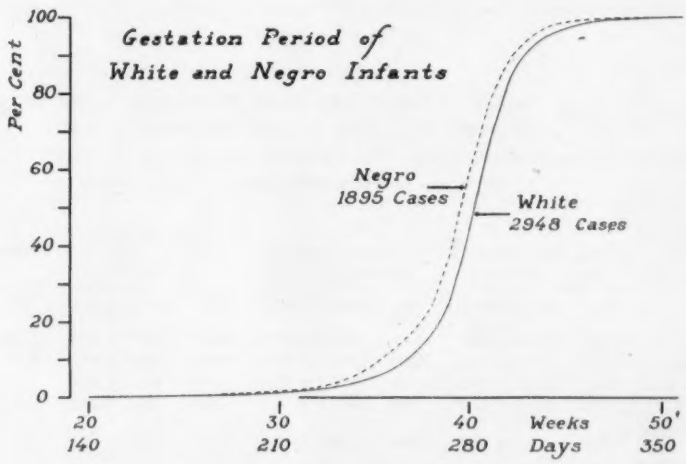

Fig. 4.—Cumulative percentage frequencies of gestation periods of white and Negro infants.

all infants whose gestation period was at least two hundred and ten days, regardless of birth weight; the second, only infants whose birth weight was at least 5 pounds and 8 ounces (2,500 Gm.), regardless of length of gestation, and the third, only those infants whose gestation period was said to have been at least two hundred thirty-eight days and whose birth weight was at least 5 pounds and 8 ounces. The means, standard deviations and tests of significance for these three groups are

also shown in table 4. In every case there is a significant race difference but not a sex difference of gestation period. This difference is of particular interest in the last group, as it indicates that the shorter gestation period observed in the Negro race is not caused by the inclusion of a large number of premature infants. When birth weights were calculated for these groups of infants of known gestation period, significant race and sex differences were again observed. The mean values

TABLE 5.—*Birth Weights of Single Live-Born White and Negro Infants of Known Gestation Period*

	Means and Standard Deviations in Pounds and Ounces															
	Last Menstrual Period Known				Gestation Period, 210 Days or More				Birth Weight, 5 Lb. 8 Oz. or More				Birth Weight, 5 Lb. 8 Oz. or More and Gestation, 238 Days or More			
		Mean ± S. D.				Mean ± S. D.				Mean ± S. D.				Mean ± S. D.		
	No.	Lb. Oz.	Lb. Oz.		No.	Lb. Oz.	Lb. Oz.		No.	Lb. Oz.	Lb. Oz.		No.	Lb. Oz.	Lb. Oz.	
White males	1,509	7 6	± 1	5	1,484	7 7	± 1	4	1,407	7 10	± 1	1	1,380	7 10	± 1	1
White females	1,439	7 2	± 1	3	1,426	7 3	± 1	2	1,334	7 5	± 0	15	1,321	7 6	± 0	15
Negro males	940	7 0	± 1	3	931	7 0	± 1	3	852	7 4	± 0	15	835	7 4	± 0	15
Negro females	955	6 12	± 1	3	934	6 12	± 1	2	840	7 0	± 0	14	818	7 1	± 0	14

	Significance of Differences Between Means											
	Diff., Oz.	"t"	"P"	Diff., Oz.	"t"	"P"	Diff., Oz.	"t"	"P"	Diff., Oz.	"t"	"P"
White males and females	4	5.7317	<0.001	4	6.3960	<0.001	5	7.3100	<0.001	4	7.3451	<0.001
White and Negro males	6	7.9661	<0.001	7	8.7611	<0.001	6	9.0603	<0.001	6	9.0696	<0.001
Negro males and females	4	4.8075	<0.001	4	4.5719	<0.001	4	4.6235	<0.001	3	4.4743	<0.001
White and Negro females	6	8.3521	<0.001	7	8.4262	<0.001	5	7.8530	<0.001	5	7.5783	<0.001

TABLE 6.—*Mean Birth Weights and Gestation Periods of Four Groups of Single Live-Born White and Negro Infants*

	White								Negro							
	Male				Female				Male				Female			
		Birth Weight		Gestation,		Birth Weight		Gestation,		Birth Weight		Gestation,		Birth Weight		Gestation,
	No.	Lb.	Oz.	Days	No.	Lb.	Oz.	Days	No.	Lb.	Oz.	Days	No.	Lb.	Oz.	Days
Cases in which last menstrual period is known	1,509	7	6	279.0	1,439	7	2	279.9	940	7	0	274.7	955	6	12	273.3
Infants of gestation 210 days or more	1,484	7	7	280.5	1,426	7	3	280.8	931	7	0	275.6	934	6	12	275.1
Infants of birth weight 5 lb. and 8 oz. or more	1,407	7	10	281.3	1,334	7	5	282.3	852	7	4	277.1	840	7	0	276.7
Infants of birth weight 5 lb. and 8 oz. or more and gestation 238 days or more	1,380	7	10	282.6	1,321	7	6	282.8	835	7	5	278.1	818	7	1	278.2

for birth weight of these groups of infants and the tests of significance are shown in table 5. Table 6 summarizes these results.

Again we wondered whether the differences observed might be due to the fact that any one group included an unusually large number of sick or diseased mothers. We resorted our cards, rejecting the record of every infant whose mother during pregnancy or labor had even minor illness or accident. There remained 2,260 infants, of whom 1,385, or about 61 per cent, were white and 875, or about 39

per cent, were Negroes. Data from these patients, who may be considered "normal," are presented in tables 7 to 12. In every case there is a significant race and sex difference in birth weight and a significant race difference in gestation period. In the group of infants weighing 5 pounds and 8 ounces or more, the two day difference in gestation period between the white male and female infants is on the borderline of significance. Examination of the data reveals that this group includes

TABLE 7.—*Frequency Distribution by Weight of Single Live-Born White and Negro Infants ("Normal" Mothers)*

Birth Weight					White		Negro		
Lb.	Oz.		Lb.	Oz.	Male	Female	Male	Female	Total
1	8	to	1	15	..	1	..	..	1
2	0	to	2	7	1	..	1	..	2
2	8	to	2	15	2	..	..	..	2
3	0	to	3	7	1	1	1	1	4
3	8	to	3	15	2	..	1	3	6
4	0	to	4	7	2	5	2	4	13
4	8	to	4	15	11	8	10	7	36
5	0	to	5	7	16	20	16	22	74
5	8	to	5	15	30	42	29	37	138
6	0	to	6	7	63	80	63	73	279
6	8	to	6	15	99	130	89	90	408
7	0	to	7	7	133	139	100	84	456
7	8	to	7	15	115	114	69	56	354
8	0	to	8	7	107	78	41	20	246
8	8	to	8	15	57	41	13	14	125
9	0	to	9	7	30	15	14	5	64
9	8	to	9	15	19	5	7	1	32
10	0	to	10	7	7	6	1	..	14
10	8	to	10	15	1	1	..	1	3
11	0	to	11	7	..	1	..	..	1
11	8	to	11	15	1	..	..	..	1
12	0	to	12	7	..	..	..	..	..
12	8	to	12	15	1	..	..	..	1
Grand total					698	687	457	418	2,260
Total by race					1,385		875		

TABLE 8.—*Mean Birth Weights of Single Live-Born White and Negro Infants ("Normal" Mothers)*

	Number of Cases	Means and Standard Deviations							
		Lb.	Oz.		Lb.	Oz.		Gm.	
White males	698	7	7	±	1	3	3,374	±	539
White females	687	7	3	±	1	1	3,260	±	482
Negro males	457	7	1	±	1	1	3,204	±	482
Negro females	418	6	13	±	1	0	3,090	±	454

Significance of Observed Differences	Number of Cases	Differences		"t"	"p"
		Oz.	Gm.		
White: males and females	1,385	4	113	4.0183	<0.001
Males: white and Negro	1,155	6	170	5.5778	<0.001
Negro: males and females	875	4	113	3.3937	<0.001
Females: white and Negro	1,105	6	170	5.8283	<0.001

a number of male infants whose reported gestation periods appear unreasonably short. However, we have in no case rejected figures because they appear unreasonable to us. It is evident that maternal health is not the decisive factor.

COMMENT

Since growth, development and age are continuous and interdependent processes, it is difficult to draw a dividing line which will serve to differentiate the premature from the mature infant. Nine calendar months or ten lunar months

TABLE 9.—*Frequency Distribution by Gestation Period of Single Live-Born White and Negro Infants ("Normal" Mothers)*

Gestation Period, Days	White			Negro		
	Male	Female	Total	Male	Female	Total
Less than 147	..	1	1	1	..	1
147-153	..	..	..	..	..	..
154-160	..	..	..	..	..	..
161-167	1	1	2	..	..	..
168-174	1	..	1	2	..	2
175-181	1	..	1	..	..	..
182-188	..	1	1	..	1	1
189-195	3	..	3	..	..	..
196-202	2	..	2	..	1	1
203-209	4	..	4	..	..	..
210-216	..	..	..	..	..	..
217-223	1	1	2	1	2	3
224-230	1	1	2	1	5	6
231-237	3	10	13	7	6	13
238-244	11	9	20	10	4	14
245-251	15	12	27	9	12	21
252-258	18	16	34	17	15	32
259-265	30	25	55	25	24	49
266-272	53	51	104	58	52	110
273-279	119	94	213	89	85	174
280-286	149	159	308	68	77	145
287-293	94	121	215	42	34	76
294-300	47	50	97	21	17	38
301-307	21	18	39	13	11	24
308-314	14	10	24	7	3	10
315-321	8	3	11	2	1	3
322-328	6	4	10	1	1	2
329-335	1	..	1	..	..	..
336-342	1	2	3	..	..	..
343-349	..	3	3	..	..	..
350 and more	1	1	2	..	1	1
Total known	605	593	1,198	374	352	726
Unknown	88	83	171	75	63	138
No menstrual period	5	11	16	8	3	11
Grand total	698	687	1,385	457	418	875

TABLE 10.—*Gestation Periods of Single Live-Born White and Negro Infants as Estimated from First Day of Last Menstrual Period ("Normal" Mothers)*

	Means and Standard Deviations, Days							
	Last Menstrual Period Known		Gestation Period, 210 Days or More		Birth Weight, 5 Lb. 8 Oz. or More		Birth Weight, 5 Lb. 8 Oz. or More and Gestation, 238 Days or More	
	No.	Mean ± S. D.	No.	Mean ± S. D.	No.	Mean ± S. D.	No.	Mean ± S. D.
White males	605	279.9 ± 20.5	593	281.6 ± 16.4	578	281.2 ± 18.3	567	282.6 ± 15.1
White females	593	281.4 ± 18.7	590	282.0 ± 16.7	560	283.2 ± 15.7	554	283.8 ± 14.8
Negro males	374	275.9 ± 19.2	371	276.9 ± 16.3	352	277.5 ± 16.4	346	278.4 ± 14.2
Negro females	352	275.6 ± 17.8	350	276.1 ± 15.7	324	277.4 ± 15.6	317	278.5 ± 13.9
White males and females	1,198	280.6 ± 19.6	1,183	281.8 ± 16.5	1,138	282.2 ± 17.1	1,121	283.2 ± 14.9
Negro males and females	726	275.8 ± 18.5	721	276.5 ± 16.5	676	277.5 ± 16.0	663	278.4 ± 14.3
	Significance of Differences Between Means							
	Diff., Days	"t"	"P"	Diff., Days	"t"	"P"	Diff., Days	"t"	"P"	Diff., Days	"t"	"P"
White males and females	1.5	1.3091	0.2-0.1	0.4	0.3484	0.8-0.7	2.0	1.9786	0.05	1.2	1.2653	0.3-0.2
Negro males and females	0.3	0.2421	0.9-0.8	0.8	0.6340	0.6-0.5	0.1	0.1006	>0.9	0.1	0.0752	>0.9
White and Negro	4.8	5.3491	<0.001	5.3	6.8271	<0.001	4.7	5.8621	<0.001	4.8	6.6378	<0.001

or two hundred and eighty days is generally accepted as the expected gestation period, but this estimate is rough and subject to wide fluctuations, even when the presumed date of fruitful coitus is known. The most widely accepted standard for differentiation is a birth weight of 2,500 Gm. or about 5½ pounds. It is our experience that the number of live-born single infants weighing between 5 and 5½ pounds (2,270 and 2,500 Gm.) is approximately equal to the number weighing

TABLE 11.—*Birth Weights of Single Live-Born White and Negro Infants of Known Gestation Period ("Normal" Mothers)*

	Means and Standard Deviations in Pounds and Ounces											
	Last Menstrual Period Known			Gestation Period, 210 Days or More			Birth Weight, 5 Lb. 8 Oz. or More			Birth Weight, 5 Lb. 8 Oz. or More and Gestation, 238 Days or More		
		Mean ± S. D.			Mean ± S. D.			Mean ± S. D.			Mean ± S. D.	
	No.	Lb. Oz.	Lb. Oz.	No.	Lb. Oz.	Lb. Oz.	No.	Lb. Oz.	Lb. Oz.	No.	Lb. Oz.	Lb. Oz.
White males	605	7 8	± 1 3	593	7 8	± 1 2	578	7 10	± 1 0	567	7 10	± 1 0
White females	593	7 3	± 1 1	590	7 4	± 1 1	560	7 5	± 0 15	554	7 6	± 0 15
Negro males	374	7 1	± 1 1	371	7 2	± 1 0	351	7 4	± 0 13	346	7 4	± 0 14
Negro females	352	6 14	± 1 0	350	6 14	± 1 0	324	7 0	± 1 0	317	7 1	± 0 13

	Significance of Differences Between Means											
	Diff., Oz.	"t"	"P"	Diff., Oz.	"t"	"P"	Diff., Oz.	"t"	"P"	Diff., Oz.	"t"	"P"
White males and females	5	4.2457	<0.001	4	4.8612	<0.001	5	4.8227	<0.001	4	4.8473	<0.001
White and Negro males	7	5.3087	<0.001	6	5.9144	<0.001	6	5.9262	<0.001	6	5.9917	<0.001
Negro males and females	3	2.7425	0.01-0.001	4	2.9707	0.01-0.001	4	3.1005	0.01-0.001	3	2.9158	0.01-0.001
White and Negro females	5	4.9393	<0.001	6	4.9979	<0.001	5	5.1957	<0.001	5	5.0782	<0.001

TABLE 12.—*Mean Birth Weights and Gestation Periods of Four Groups of Single Live-Born White and Negro Infants ("Normal" Mothers)*

	White						Negro					
	Male			Female			Male			Female		
		Birth Weight	Gestation,		Birth Weight	Gestation,		Birth Weight	Gestation,		Birth Weight	Gestation,
	No.	Lb. Oz.	Days	No.	Lb. Oz.	Days	No.	Lb. Oz.	Days	No.	Lb. Oz.	Days
Cases in which last menstrual period is known	605	7 8	279.9	593	7 3	281.4	374	7 1	275.9	352	6 14	275.6
Infants of gestation 210 days or more	593	7 8	281.6	590	7 4	282.0	371	7 2	276.9	350	6 14	276.1
Infants of birth weight 5 lb. and 8 oz. or more	578	7 10	281.2	560	7 5	283.2	351	7 4	277.5	324	7 0	277.4
Infants of birth weight 5 lb. and 8 oz. or more and gestation 238 days or more	567	7 10	282.6	554	7 6	283.8	346	7 4	278.4	317	7 1	278.5

less than 5 pounds, each weight group containing about 5 per cent of the total number of births. It is difficult to compare statistics unless the standards used are approximately the same and are definitely stated.

It is important to examine the standards and to inquire not only what the expectation should be but how large a deviation from these standards should be permitted before a diagnosis of prematurity is made. It is extremely doubtful whether one may use the same standards for the diagnosis of prematurity for single and for multiple births. Many twins will fall into the group who, born at

term, are well developed and well nourished but small. Until the question has been examined more carefully, it has seemed to us a safer procedure to include in a discussion of standards of prematurity only single births of live-born infants.

No single criterion will serve to describe a syndrome as complex as prematurity. In making the diagnosis, anthropometric measurements, roentgenograms of centers of osseous development and studies of respiratory rate and erythropoiesis are of great assistance. The value of such studies cannot be overestimated, but the fact that few institutions and no private homes are equipped to offer opportunities for them as well as the necessity for the minimum of handling of very small infants make them of little practical value as routine procedure.

Birth weight, while not necessarily an index of the time spent by an infant in utero, is a fairly satisfactory measure of its ability to survive. Moreover, the weighing of infants at birth is a universal practice, easily and quickly accomplished with sufficient accuracy by even an untrained attendant. If a definition of prematurity is based on birth weight alone, infants will be included who, although born before term, have attained a satisfactory state of growth and development for their time in utero, infants born before term whose development has been faulty because of fetal, placental or maternal abnormality, infants born approximately at term who are small but well developed and well nourished and, finally, infants born at term whose development has been unsatisfactory and who are thin and badly nourished. Infants will be excluded who, although born before term and premature from the point of view of age, nevertheless have attained a satisfactory weight. Those infants whose growth but not development has been satisfactory will also be excluded. It must be remembered that in the presence of certain serious congenital abnormalities, such, for instance, as absence of some portion of the body or hydrocephalus, weight alone cannot be used as an index of prematurity.

Although the age of the fetus is in general an excellent index of its ability to survive after birth, a diagnosis of prematurity based on gestation period alone is unsatisfactory because of the difficulty of fixing the exact date of conception. Certain infants born before the usual time make a satisfactory adjustment to extrauterine life. When the gestation period is unknown, the infant is of course classified on the basis of development alone.

In defining prematurity there must be considered two fundamental concepts: time in utero and the state of physical growth and development. Infants weighing more than 5 pounds and 8 ounces (2,500 Gm.) at birth are almost always mature enough not to need special care. Infants weighing less than 5 pounds (2,270 Gm.) are generally inadequately equipped for their new environment and require special care. The classification of infants whose birth weights lie between 5 pounds and 5 pounds and 8 ounces (2,270 and 2,500 Gm.) is more difficult. Numerically, in our series this group was as large as the total group weighing less than 5 pounds. In this intermediate group, gestation period, sex and race become important factors in the determination of the maturity of the infant and the type of treatment needed. Negro infants, especially girls, with birth weights of 5 pounds to 5 pounds and 8 ounces (2,270 to 2,500 Gm.) are more mature than white infants of the same weight. The average figure for gestation period for both white and Negro infants in this weight group is two hundred and sixty-seven days. This is closer to the expected length of gestation for the Negro infants, and therefore this weight group probably includes a greater percentage of mature Negro infants. We would conclude, then, that in borderline cases the determination of the maturity of an infant can be rendered more accurate by the consideration of race, sex and gestation period.

SUMMARY

A group of 5,686 consecutive live-born single infants was studied for the purpose of comparing the influence of race and sex on birth weight and gestation period. This group included 3,389 white infants, of whom 1,731 were male and 1,658 were female, and 2,297 Negro infants, of whom 1,144 were male and 1,153 were female. The gestation period, as estimated from the first day of the last menstrual period, was known for 4,843 of these infants. Of these 4,843 infants, 1,509 were white boys, 1,439 white girls, 940 Negro boys and 955 Negro girls.

The mean birth weight of the white boys was 7 pounds and 6 ounces (3,345 Gm.); of the white girls, 7 pounds and 2 ounces (3,232 Gm.); of the Negro boys, 6 pounds and 15 ounces (3,147 Gm.) and of the Negro girls, 6 pounds and 11 ounces (3,033 Gm.). The race and sex differences in birth weight were in every case of great statistical significance.

The mean gestation period of the white boys was two hundred and seventy-nine days, of the white girls two hundred and seventy-nine and nine tenths days, of the Negro boys two hundred and seventy-four and seven tenths days and of the Negro girls two hundred and seventy-three and three tenths days. The differences in gestation period between male and female infants of the same race were not significant. The difference between gestation periods of white and Negro infants was of great statistical significance.

In order to determine whether the observed differences were a true racial characteristic or were due to the occurrence of a larger number of premature infants in the Negro race, the same calculations were made for three other groups. A significant race and sex difference in average birth weight and significant race differences in average gestation period were found within these three groups. These groups were as follows: (1) infants of at least two hundred and ten days' gestation period; (2) infants whose birth weight was at least 5 pounds and 8 ounces (2,500 Gm.), and (3) infants whose gestation period was at least two hundred and thirty-eight days and whose birth weight was 5 pounds and 8 ounces. These groups were selected according to current criteria of viability or maturity.

Significant differences were also found among infants whose mothers had had no illness or accident during pregnancy or labor.

It seems logical to conclude that race and sex should be considered in the definition of prematurity. This is particularly true for the borderline cases.

It may be practical to establish separate weight standards for the white and Negro races. Five pounds and 8 ounces, or 2,500 Gm., may be considered the lower limit of normal for the white infants and 5 pounds, or 2,300 Gm., as the lower limit of normal for the Negro infants.

1305 West Erie Avenue.
2423 Ingleside Place.
1 Dexter Lane.

PRIMARY AND SECONDARY SEXUAL CHARACTERISTICS

STUDY OF THEIR DEVELOPMENT IN MALES FROM BIRTH THROUGH MATURITY, WITH BIOMETRIC STUDY OF PENIS AND TESTES

LIEUTENANT WILLIAM A. SCHONFELD
MEDICAL CORPS, ARMY OF THE UNITED STATES

In view of the complexity of the process of growth and maturation, it is not surprising to find great variations among normal boys as to the time of onset of pubescence, the rate of development and the ultimate size of the genitalia. This study was undertaken in an attempt to ascertain the actual variations among normal boys and men as to the size of the testes and of the penis and the degree of development of secondary sexual characteristics.

The primary sexual organs are essentially the gonads, but we shall accept the broader classification, which includes all the organs required for procreation. These in males are the testes, the epididymides, the seminal vesicles, the prostate and the duct systems. In children these primary sexual organs differ considerably in size and structure from those of adults, since they do not as yet exercise their specific function. They are maintained in a quiescent state, without appreciable growth after infancy, until the onset of pubescence, when there is a rapid growth of the genitalia with production of spermatozoa at puberty. Following this, there is a stage of postpubescent maturation, called adolescence, ending with maturity. The curves for relative weight of the genitalia and of the body during these stages of development have been well presented by Scammon.[1] However, there is a great variation in the age at which the pubescent spurt begins and in the rate of development during pubescence, as well as individual differences in the initial and final sizes of the genitalia. This creates a wide range of normal size and functional state of the gonads in children at any age, particularly between 10 and 18 years. The secondary sexual characteristics, such as deep voice, hirsuties, development of muscles and bones and emotional maturation, which are largely dependent on the function of the testes, begin to develop with pubescence and end with full maturity and thus are also subject to great variation.

To evaluate this variation in the development of normal children, the genital status of about 1,500 normal white boys and men from birth to 25 years of age was studied and the accumulated data were statistically analyzed. The subjects examined were from general pediatric, medical, dental, otolaryngologic, traumatic and special follow-up clinics and wards at the Neurological Institute of New York, Vanderbilt Clinic, Babies and Presbyterian Hospitals of Columbia-Presbyterian Medical Center, Morrisania City Hospital and Mount Sinai Hospital. From this wide source of patients we were assured of a good sample of the general population of all nationalities and economic statuses in New York. The table shows the number of boys and men examined in each age group. The stated age is recorded according to the birthday preceding the examination.

Care was taken to exclude boys known or suspected to be suffering from an endocrinopathy or other abnormality associated with genital development. Although the nationality of each

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Statistical analysis by Gilbert Beebe, Ph.D., New York.

From the Columbia-Presbyterian Medical Center, Morrisania City Hospital and Mount Sinai Hospital.

1. Harris, J. A.; Jackson, C. M.; Paterson, D. G., and Scammon, R. E.: The Measurement of Man, Minneapolis, University of Minnesota Press, 1930, p. 215.

patient and of his parents was recorded, no attempt was made to analyze the data on a racial basis, because review of the literature (summarized graphically in figure 1) revealed no appreciable variation in the size of the testes in the various nationalities studied and reported,[2] although the age of onset of pubescence probably varies. The only possible exception

Number of Observations for Length and Circumference of the Penis and for Volume of the Testes, by Age

Age	Number of Subjects		
	Penis		Testes, Volume
	Length	Circumference	
0- 5 months	125	125	247
6-11 months	51	51	101
1 year	50	50	98
2 years	50	50	98
3 years	50	50	100
4 years	50	50	98
5 years	50	50	96
6 years	50	50	98
7 years	50	50	98
8 years	50	50	100
9 years	50	50	96
10 years	82	81	162
11 years	91	91	175
12 years	93	92	186
13 years	104	104	204
14 years	121	121	242
15 years	101	100	201
16 years	76	76	150
17 years	61	61	122
18 years	40	40	79
19 years	31	31	62
20-25 years	54	55	110
Total	1,480	1,478	2,923

2. (*a*) Freeman, W.: The Weight of the Endocrine Glands: Biometrical Studies in Psychiatry, Human Biol. **6**:489, 1934. Pearl, R.; Gooch, M., and Freeman, W.: A Biometric Study of the Endocrine Organs in Relation to Mental Disease, ibid. **7**:555, 1935. Pearl, R.; Gooch, M.; Miner, J. R., and Freeman, W.: Studies on Constitution: IV. Endocrine Organ Weights and Somatological Habitus Types, ibid. **8**:92, 1936. Scammon, R. E.: Growth of the Human Reproductive System, Proceedings of the Second International Congress for Sex Research, 1930, p. 118. (*b*) Eberth, C. J.: Die männlichen Geschlechtsorgane, in von Bardeleben, K.: Handbuch der Anatomie des Menschen, Jena, G. Fischer, 1904, vol. 2, pt. 2. Gundobin, N. P.: Die Besonderheiten des Kindesalters, Berlin, Allgemeiner medizinischer Verlag, 1912. Henle, F. G. J.: Handbuch der systematischen Anatomie des Menschen, Braunschweig, F. Vieweg u. Sohn, 1873, vol. 2, p. 362. Leupold, E.: Beziehungen zwischen Nebennieren und männlichen Keimdrüsen, Veröffentl. a. d. Geb. d. Kriegs- u. Konst. Path. **4**:1, 1920. Mühlmann, M.: Wachstum, Altern und Tod. Ueber die Ursache des Alterns und des Todes, Ztschr. f. d. ges. Anat. (pt. 3) **27**:1, 1927. Mita, G.: Physiologische und pathologische Veränderungen der menschlichen Keimdrüse von der fötalen bis zur Pubertatszeit, mit besonderer Berücksichtigung der Entwicklung, Beitr. z. path. Anat. u. z. allg. Path. **58**:554, 1914. Roessle, R., and Roulet, F.: Mass und Zahl in der Pathologie, Berlin, Julius Springer, 1932, p. 83. Schilf, F.: Die quantitativen Beziehungen der Nebennieren zum übrigen Körper, Ztschr. f. Konstitutionslehre **8**:507, 1922. Schultze, W. H.: Männliche Geschlechtsorgane, in Brüning, H., and Schwalbe, E.: Handbuch der allgemeinen Pathologie und der pathologischen Anatomie des Kindesalters, Wiesbaden, J. F. Bergmann, 1913, vol. 2, pt. 1. Sitsen, A. E.: Zur Kenntnis des Normalen, Ztschr. f. Konstitutionslehre (Ztschr. f. d. ges. Anat.) **16**: 308, 1931. Stieve, H.: Harn- und Geschlechtsapparatus, in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1930, vol. 7, pt. 2. (*c*) Mackevičaité-Lašiené, J.: Average Weight and Size of Endocrine Glands in Lithuanians, Acta med. Fac. Vytauti Magni Univ. Kaunas **3**:289, 1936. (*d*) Wwedenski, A. A.: Die Hoden und Samenblasen der Kinder, Inaug. Dissert., St. Petersburg, 1900; cited by Wagensteen.[2f] (*e*) Oiye, T.: Statistische und histologische Hodenstudien, Mitt. ü. allg. Path. u. path. Anat. **4**:425, 1928. Morioka, Y.: Position, Diameter and Weight of Human Testes and Certain Observations in Vas Deferens and External Cremasteric Muscles, Okayama-Igakkai-Zasshi **48**:2716, 1936.

is the Japanese, who seem to have appreciably smaller testes as adults. It must be remembered that the data represented by these curves are not entirely comparable, since some of the authors weighed both testes together, some without and others with the epididymides; so it was necessary to calculate arbitrarily the weight of one testis alone before it could be included in the data. Another experimental factor which may create such variations as are noted in the curves is the degree of drying and fixation of the testes weighed by the various observers, since, as Bischoff [3] has pointed out, by weight a fresh testis is only about 18 per cent tissue and 82 per cent water. It will suffice to state that about 85 per cent of the boys and men were of the first generation, born in the United States and an additional 13 per cent were second generation Americans; the remaining 2 per cent, as well as the ancestors of the American-born subjects, were born in practically every country of Europe, in Canada and in some South American countries. In addition, it was noted that there was a fairly equal distribution among religions.

In presenting the results of this investigation of the normal genital development of boys [4] no attempt will be made to review the extensive literature on the

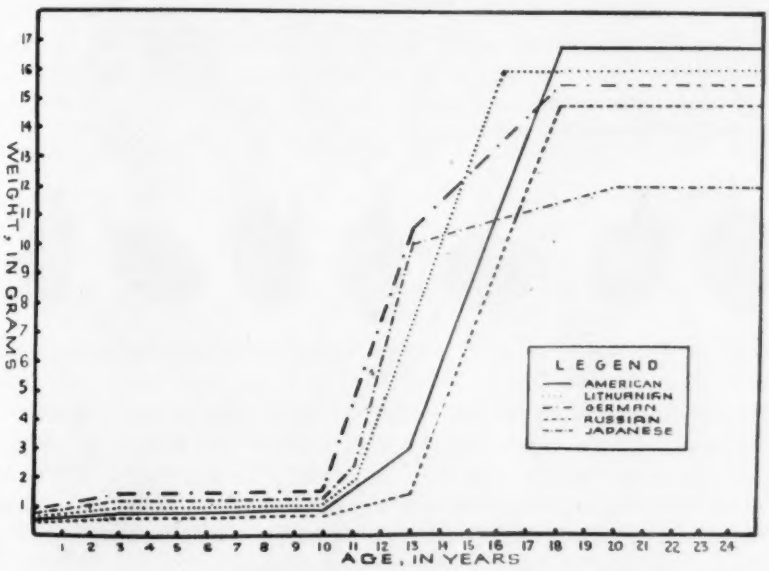

Fig. 1.—Weight of testis according to nationality, based on values obtained from a review of the literature listed in footnote 2 (*a*, American; *b*, German; *c*, Lithuanian; *d*, Russian; *e*, Japanese).

Endo, M.: Ueber das Volumen des Hodenparenchyms bei den japanischen Kindern, Okajimas Folia anat. japon. **17**:451, 1938. (*f*) Vierordt, H.: Anatomische, physiologische und physikalische Daten und Tabellen, Jena, Gustav Fischer, 1906, p. 57. Wangensteen, O. H.: The Surgery of the Undescended Testis, Surg., Gynec. & Obst. **54**:219, 1932. Cooper, A.: Observations on the Structure and Diseases of the Testis, London, J. Churchill, 1830. Smith, G. G., in Cobat, H.: Modern Urology in Original Contribution by American Authors, Philadelphia, Lea & Febiger, 1936, vol. 1, p. 397.

3. Bischoff, E.: Ztschr. f. rat. Med. **20**:75, 1863.

4. (*a*) Greulich, W. W.; Day, H. G.; Lachman, S. E.; Wolfe, J. B., and Shuttleworth, F. K.: Handbook of Methods for the Study of Adolescent Children, Monographs of the Society for Research in Child Development, serial no. 15, 1938, vol. 3, no. 2. (*b*) Peter, K.: Männliche kindliche Geschlechtsorgane, in Peter, K.; Wetzel, and Heidrich: Handbuch der Anatomie des Kindes, Munich, J. F. Bergmann, vol. 2, pt. 1. (*c*) Schmidt-Voigt, J.: Der gegenwärtige Eintritt und die Acceleration der Pubertätsentwicklung dei der männlichen Jugend einer Grossstadt, Ztschr. f. Kinderh. **61**:548, 1940.

histologic development.[5] I shall merely mention the points which aid in the evaluation of the data accumulated. The reliability and validity of the method of measurements used had been established, and the data accumulated on measuring the testes and penises of about 1,500 boys and men were statistically analyzed in great detail in a previous communication.[6]

PRIMARY SEXUAL CHARACTERISTICS

Testes.—In discussing the growth of the testes, one must consider not only their own change in size but also their relationship to the epididymides. In a newborn boy the epididymis, which is about equal in size to the testis, is completely separated from it, the body being weakly attached while the head is completely free.[7]

At about 2 years of age the epididymis and testis are closer together but the head is still free. During pubescence both grow but the testis grows at a more rapid rate, so that during early pubescence the epididymis may be only one-third or one-quarter the size of the testis; later its relative size decreases, until in adult life it is only one-ninth the size of the testis.[8] During the period of rapid growth the epididymis becomes more closely bound to the testis, so that at times it is difficult to evaluate the exact size of the testicle alone. When this problem arises in the longitudinal study of an individual, no attempt is made to isolate the testis but the volume of the epididymal testicular mass is recorded as a unit.

Fig. 2.—Position of testis in relation to epididymis during pubescence.

In a child the testis is ovoid and about the same shape as in an adult.[4b] As to its position, the literature states that during childhood the testicle is vertical while in adulthood the upper pole is superior and lateral. This is true in most cases, but it is not uncommon to find the testis during pubescence in some unusual position, as noted in figure 2. Latarjet,[9] Poirier and Charpy[10] and Campbell[11] also noted some of these positions in the subjects they studied.

Histologically the testis undergoes several changes during the various stages of development.[12] As the length and diameter of the tubules increase and lumens

5. (*a*) Spangaro, S.: Ueber die histologischen Veränderungen des Hodens, Nebenhodens und Samenleiters von der Geburt an bis zum Greisenalter, Anat. Hefte (pt. 1) **18**:593, 1902. (*b*) Rowlands, I. W., and Brambell, F. W. R.: Development and Morphology of the Gonads of the Mouse: The Post-Natal Growth of the Testis, Proc. Roy. Soc., London, s.B **112**: 200, 1933. (*c*) Greulich and others.[4a] (*d*) Peter.[4b]

6. Schonfeld, W. A., and Beebe, G.: Normal Growth and Variation in the Male Genitalia from Birth to Maturity, J. Urol. **48**:759, 1942.

7. Poirier, P.: Kystes de l'epididyme, Rev. de chir., Paris **10**:861, 1890.

8. Peter.[4b] Poirier.[7]

9. Testut, L., and Latarjet, A.: Traité d'anatomie humaine. Appareil uro-génital. Péritoine, ed. 8, Paris, Gaston Doin, 1931, vol. 5, p. 152.

10. Poirier, P., and Charpy, A., in Testut, J. L.: Traité d'anatomie humaine, anatomie descriptive, ed. 4, Paris, O. Doin, 1901, vol. 5, p. 225.

11. Campbell, M. F.: Pediatric Urology, New York, The Macmillan Company, 1937, vol. 1, p. 310.

12. Jaffe, R., and Berberich, F.: Hoden, in Hirsch, M.: Handbuch der inneren Sekretion, Leipzig, Curt Kabitzsch, 1927, vol. 1, pt. 2, p. 197. Greulich and others.[4a] Peter.[4b] Spangaro.[5a]

begin to form and eventually spermatogonia are transformed to spermatozoa, there is a relative reduction in the amount of intertubular connective tissue, so that the testis becomes temporarily softer. Interstitial cells of Leydig soon appear in the connective tissue for the first time since infancy, when they were present as a result of the maternal pituitary or chorionic gonadotropic stimulation; they disappear after four to six weeks but reappear at pubescence as result of the boy's own pituitary gonadotropic hormones.

Although the literature[2] contains many reports on postmortem measurements and weights of the testes, they are merely the average values at each age (fig. 1) and thus are of no appreciable help in evaluating the genital status of an individual.[13]

For each of the 1,500 boys and men[14] examined the volume of each testicle was determined by palpating the testicular mass with one hand while the other ran through a graded series of hard rubber models (fig. 3 *D*) the volumes of which were known. When a model was found which seemed to have the same volume as the testicle, the observation was recorded. In recording, however, the median, or middle, value of 3 such observations was taken.

In preparing the standards a large number of postmortem specimens were obtained and utilized in the construction of a set of wax models. The volume of each model was then obtained by water displacement and a graded series selected. The volumes of the models used were 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 18 and 25 cc. At each point in the range of volume the smallest perceptible difference was taken into account in selecting the models for inclusion in the standard set. These models were then reproduced in rubber and their volumes rechecked by water displacement (fig. 3 *E*).

In analyzing the data to ascertain the relative sizes of the right and left testes, it was found that in 23 per cent of the boys the right testis was larger than the left while in 22 per cent the right testis was smaller than the left and in 55 per cent the right and left testes were equal in size. These figures confirm some observations in the literature and contradict others which claim that the right testicle is always larger than the left.

The curves for growth of the testes (fig. 4) were prepared by plotting the tenth, fiftieth and ninetieth percentiles of the cumulative percentage frequency distributions at various ages, as described in a previous communication.[6] The line connecting the fiftieth percentile, or median,[15] points indicates the trend of growth, while the area between the lines joining the first decile points and the ninth decile points indicates the range of size of 80 per cent of the testes measured.

The median growth curve shows a slight growth of the testes during the first two years followed by a prolonged quiescent period until the age of 11 years, when there is a rapid spurt of growth, reaching its maximum at about 17 years. During this period of active growth the vertical distance between the first and ninth deciles lengthens rapidly. This is due, as previously explained, to the wide variation of the date of onset of pubescence and the rate of genital maturation. A realization of this great variation is essential to evaluate the genital status of an individual.

13. (*a*) Reich, H.: Klinische Testikelmessungen bei Kindern, Jahrb. f. Kinderh. **105**:290, 1924. (*b*) Shorohowa, A. A.: Elements of the Study of Sterility in Man, paper read at the Union of Socialist Soviet Republics Congress on Genetics and Selection, Leningrad, Jan. 15, 1929, unpublished paper (courtesy of R. L. Dickinson). (*c*) Shuttleworth, F. K.: Adolescent Period (Graphic and Pictorial Atlas), Monographs of the Society for Research in Child Development, serial no. 16, 1938, vol. 3, no. 3. (*d*) Crampton, C. W.: Physiological Age: A Fundamental Principle, Am. Phys. Educat. Rev. **13**:141, 214, 268 and 345, 1908; (*e*) Influence of Physiological Age on Scholarship, Psychol. Clin. **1**:115, 1907; (*f*) Physiological Age, Pedagog. Seminary **15**:230, 1908. (*g*) Footnote 2. (*h*) Footnote 2 *a*.

14. Although 1,500 subjects were examined, complete data were not obtained on all (details are given in the table).

15. The median of a series of measurements is that point in its frequency distribution where there are equal numbers of members of the series larger and smaller than this measurement.

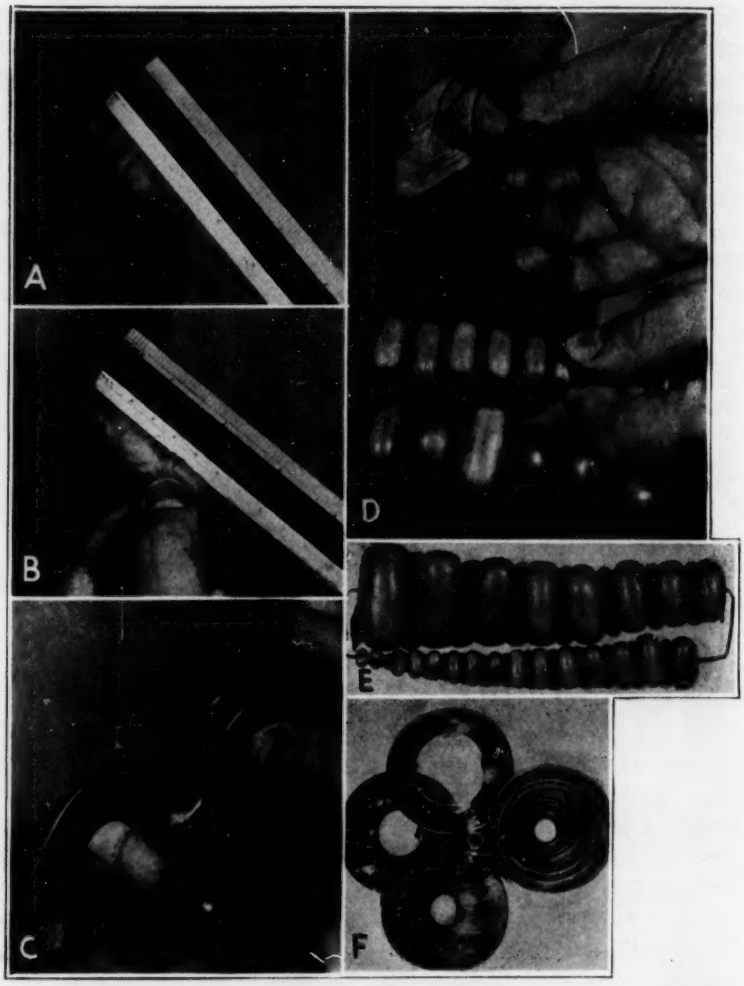

Fig. 3.—Methods of evaluating the genital status. *A*, measurement of length of the relaxed penis; *B*, measurement of length of the stretched penis; *C*, measurement of the circumference; *D*, comparison of a testis with a standard of known volume; *E*, orchidometer; *F*, gage for measurement of circumference.

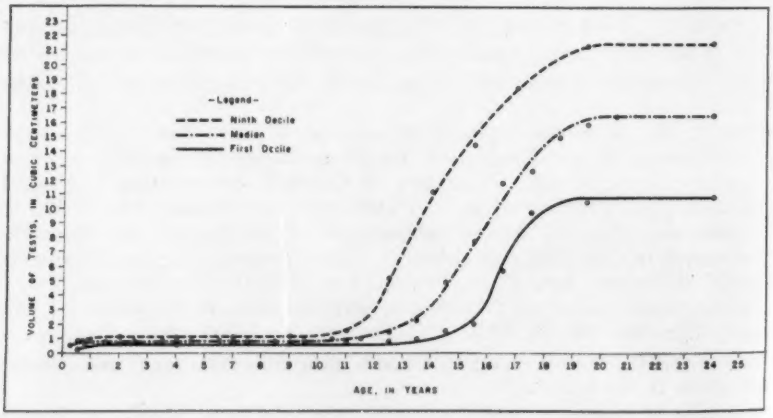

Fig. 4.—Curve for growth of the testis in volume from birth to maturity.

Through the use of growth curves of the testes or of frequency distribution curves [6] of the various sized testes at each age one may more readily evaluate the genital status of an individual and ascertain whether the volumes of his testicles are within the range of normal for his age.

Penis.—The literature is wholly inadequate as to the normal range of size of the penis, as has been pointed out by Dickinson,[16] who investigated this field thoroughly. The only original measurements on children were published by Zwineff [17] and Kubitschek,[18] and these are inadequate. For adults there are several other references,[19] but the only comprehensive work has been done by Loeb.[20]

There are several references in the literature [21] confirming Piersol's [22] observation that the size of the normal penis is in no way related to the general body build. This is also borne out by our observations on the adolescent boys.

The data accumulated were not adequate to permit any conclusions as to the racial variations in the size of the penis; but one fact that we did ascertain, which was also observed by Dickinson, was that the proportionate lengths of the relaxed flaccid penis and of the erect penis vary in different races.

In a newborn infant the corpus spongiosum urethrae is relatively larger than the corpora cavernosa and continues to grow somewhat in length during the first four or five years of life. During pubescence, accompanying the growth of the testes, there is extensive growth of the corpora cavernosa and of the corpus spongiosum,[23] so that the penis grows not only in length but in girth. Associated with this rapid growth of the penis, the glans becomes turgescent and the long prepuce of infancy frequently recedes.[4a,b]

The penis is primarily an organ of copulation, so that its true physiologic size would be gaged by measurement of the erect phallus. Since it was not feasible to obtain observations on the erect penis on a scale sufficient for this study, my associate and I had to resort to indirect evaluations of these measurements. The dorsal length from the pubopenal skin junction to the tip of the glans was measured with an ordinary centimeter rule, first for the relaxed, flaccid penis (fig. 3*A*) and then for the fully stretched penis (fig. 3*B*). Each measurement was taken three times, and the median, or middle, value was recorded. It was soon found that the length of the relaxed flaccid penis varied a great deal as a result of environmental factors and suprapubic obesity and was wholly unreliable as a guide to the genital status [24]; therefore only the length of the fully stretched organ has been extensively studied. In a previous publication [6] it had been ascertained that the length of the fully stretched penis is practically identical with the length of the erect phallus and is thus acceptable as a pertinent measurement.

16. Dickinson, R. L.: Human Sex Anatomy, Baltimore, Williams & Wilkins Company, 1933, pp. 71-84.

17. Zwineff: Die ausseren Geschlechtsorgane der Kinder, Inaug. Dissert., St. Petersburg, 1900; cited by Gundobin.[2b]

18. Kubitschek, P. E.: Sexual Development of Boys with Special Reference to Appearance of Secondary Sexual Characters and Their Relationship to Structural and Personality Types, J. Nerv. & Ment. Dis. **76**:425, 1932.

19. (*a*) Cecil, A. B., in Cabot, H.: Modern Urology in Original Contributions by American Authors, Philadelphia, Lea & Febiger, 1936, vol. 1, p. 115. (*b*) Charpy, A.: Cours de splanchinologie. Organes génito-urinaires, Toulouse, Cassanfils, 1890, p. 344. (*c*) Krause, C. F. T., in Krause, W.: Handbuch der menschlichen Anatomie, Hannover, Hahn, 1876, vol. 2, p. 961. (*d*) Waldeyer, H. W. G.: Das Becken (Topographisch-anatomisch mit besonderer Berücksichtigung der Chirurgie und Gynäkologie dargestellt), Bonn, M. Cohen & Sohn, 1899. (*e*) Testut and Latarjet.[9]

20. Loeb, H.: Harnröhrencapacität und Tripperspritzen, München. med. Wchnschr. **46**: 1016, 1899.

21. Campbell.[11] Dickinson.[16]

22. Piersol, cited by Dickinson.[16]

23. Brack, E.: Anatomische Untersuchungen über den menschlichen Penis, über sein Wachstum und seine Alterserscheinungen, Ztschr. f. urol. Chir. **15**:162, 1924.

24. Schonfeld, W. A.: Management of Male Pubescence, J. A. M. A. **121**:177 (Jan. 16) 1943.

In evaluating the girth or circumference the same problem arose, to obtain a measurement that would correlate with the circumference of the erect organ. For the purpose of this investigation the circumference of the fully stretched flaccid penis was taken as that of the smallest of a graded series of rings or washers (fig. 3*C*), which would slip over the glans and shaft with ease. Rings were used rather than a tape to facilitate the determination of this circumference. The rings were 3, 4, 4.5, 5, 6, 7, 8, 9, 10, 12 and 14 cm. in inside circumference (fig. 3*F*). Again 3 observations were made and the median recorded. The rings were run through in both directions, and their marking is sufficiently unobtrusive to justify the conclusion that the 3 observations were independent in that none was biased by a previous one; and, since the reliability and validity of these measurements have been proved, they may be accepted for statistical analysis. In the previous communication[6] it had been proved that there is a definite correlation between the circumference of the flaccid and erect phallus expressible by a mathematical equation,[25] but practically it was found that the erect penis was about two ring sizes[26] larger than the flaccid penis. Thus, a flaccid stretched penis with a circumference of 5 cm. would be 7 cm. in girth when erect, while a flaccid penis with a circumference of 9 cm. would be about 12 cm. in girth when erect.

The growth curves (figs. 5 and 6) for both the length and the circumference of the fully stretched penis were constructed in the same way as the curves for the testes, on the basis of the cumulative frequency curves of the length and the circumference of the penis for the 1,500 boys and men studied. These curves may be utilized to evaluate the genital status of an individual by comparing the measurements of his penis with that of other normal boys and men of the same age. However, the growth characteristics of the three measurements vary. Although they all show a rapid phase of growth starting at about 10½ or 11 years of age, only the curve for length of the penis shows a period of moderately rapid growth extending from birth to above 5 years of age. This is probably an expression of longitudinal growth of the body rather than a specific genital growth and is due to the growth of the corpus spongiosum urethrae.

Scrotum.—The scrotum of a newborn child is a flaccid, dark red sac with a conspicuous raphe and wrinkled skin covered with a sparse growth of lanugo. This form of scrotum according to Peter[4b] persists until the boy is 7 to 10 months of age, when it becomes less flaccid and the form changes so that the width at the proximal end is greater than at the distal end. There is no further change in the scrotum until the onset of pubescence, when, as a result of the rapid growth of the testes and epididymides, there are a progressive increase in size of the scrotum and distention of the distal portion of the sac to accommodate its contents, so that the proximal end becomes relatively narrower.

We shall not discuss the development of the spermatic ducts, seminal vesicles and ejaculatory ducts,[27] as no attempt was made to evaluate them in this series.

Prostate.—Although the prostate gland is one of the most sensitive indicators as to the presence or absence of androgenic hormone, it is only too rarely examined and evaluated in pubescence. Unfortunately, our data on the development of the prostate are not as thorough as we should like, but such facts as have been accumulated are here presented (fig. 7). During infancy and early childhood no prostate is palpable by rectal examination, but frequently prior to the onset of pubescence or in early pubescence a small, apparently single-lobed structure is

25. Means for the value of the circumference of the erect penis corresponding to those for the circumference of the stretched penis of 5, 6, 7, 8, 9 and 10 cm. are well approximated if the latter values are multiplied by 1.36, 1.28, 1.34, 1.37, 1.30 and 1.30 respectively. For the entire range this ratio is 1.34.

26. Ring sizes are 3, 4, 4.5, 5, 6, 7, 8, 9, 10, 12 and 14 cm.

27. Fischer, A. W.: Nebenhoden, Samenwege, Prostata, akzessorische Geschlechtsdrüsen, in Hirsch, M.: Handbuch der inneren Sekretion, Leipzig, Curt Kabitzsch, 1927, vol. 1, pt. 2 Peter.[4b]

palpable at the neck of the bladder. It is a spherical body with its width greater than its length. With the advent of pubescence the monolobar organ increases progressively in size as a result of enlargement of the five undifferentiated lobes; but at puberty, because of relatively greater enlargement of the two lateral lobes, a groove appears between them, over which the posterior lobe fits like a thin cap but does not prevent a median furrow from becoming palpable per rectum. The

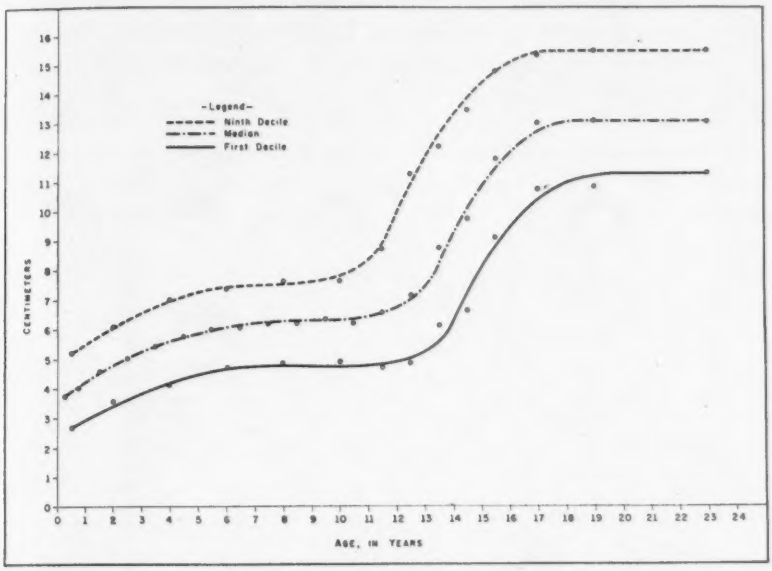

Fig. 5.—Curve for growth of the penis in length from birth to maturity.

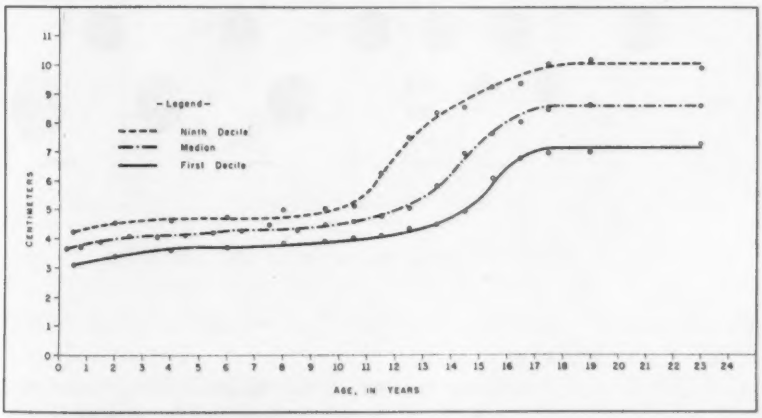

Fig. 6.—Curve for growth of the penis in circumference from birth to maturity.

anterior lobe at the same time shrinks into insignificance, while the middle lobe takes part in the general increase in size.[28] A short time after this a secretion may be massaged out of the prostate. The microscopic constituents[29] of the earliest prostatic secretion are being studied at the time of writing this report.

28. Lowsley, O. S.: (*a*) Personal communication to the author; (*b*) The Prostate Gland, in Oxford Loose Leaf Surgery, New York, Thos. Nelson & Sons, 1935, vol. 3, pt. 746; (*c*) Human Prostate in Youth, M. Rec. **88**:383, 1915; (*d*) Development of Human Prostate, Am. J. Anat. **13**:299, 1912.

29. Röhlich, K.: Ueber die Prostatasekretion, Ztschr. f. mikr.-anat. Forsch. **43**:451, 1938.

Lowsley,[28] Moore [30] and others [31] have made detailed histologic studies of the prostate in children of all ages and have shown that in newborn infants the prostate has reached a high stage of development and progresses further in the next four to seven days probably as a result of androgenic stimulation from the interstitial cells of the child's own testes, which have developed in response to the chorionic gonadotropins reaching the fetal circulation. In the next four to six weeks the hyperplastic acini involute and are maintained in this state of quiescence until the advent of pubescence, when the testes again produce androgenic hormones and the prostatic acini again become hyperplastic and the lobes develop as previously indicated. The prostate obviously could not be accurately measured in this series, but

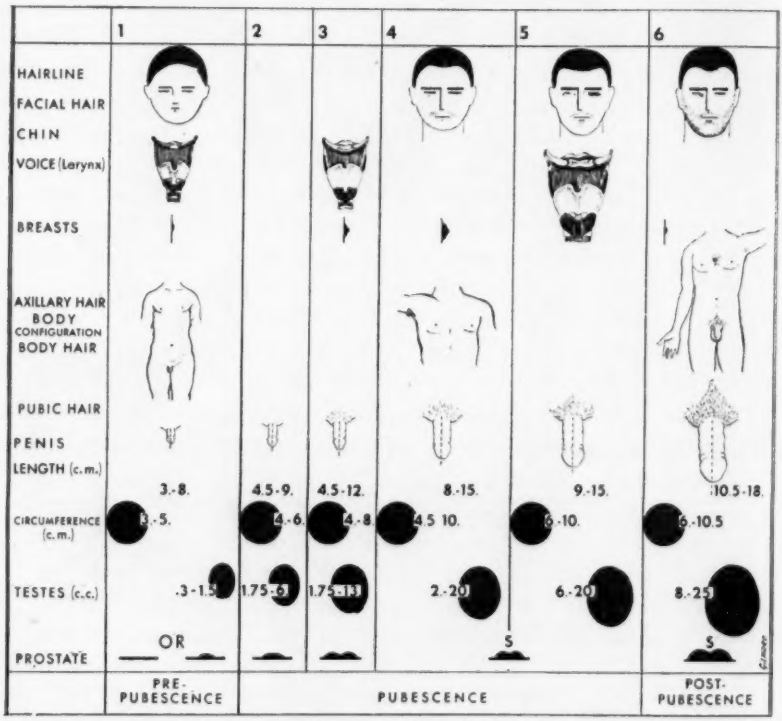

Fig. 7.—Stages of sexual development and maturation.

according to Scammon [1] and other observers [32] its weight curve corresponds to the growth curve of the genitalia.

Sex Hormones.—The hormone content of the blood and urine of children has been studied by numerous investigators,[33] but unfortunately the available technics

30. Moore, R. A.: (*a*) The Histology of the Newborn and Prepuberal Prostate Gland, Anat. Rec. **66**:1, 1936; (*b*) Evolution and Involution of the Prostate Gland, Am. J. Path. **12**:599, 1936.

31. (*a*) Van Duzen, R. E.; Looney, W. W., and Duncan, C. N.: Development of Prostate, J. Urol. **41**:473, 1939. (*b*) Geissendörfer, R.: Prostata, Leipzig, Johann Ambrosius Barth, 1940. (*c*) Ljachowski: Ueber die Veränderungen der Prostata im Kindesalter, Inaug. Dissert., St. Petersburg, 1903; cited by Gundobin.[2b] (*d*) Peter.[4b]

32. Thompson, T., in Holmes, T., and Hulke, J. W.: A System of Surgery, Theoretical and Practical, ed. 3, New York, William Wood & Co., 1883, vol. 3, p. 284. Peter.[4b]

33. Oesting, R. B., and Webster, B.: Sex Hormone Excretion of Children, Endocrinology **22**:307, 1938.

are not sufficiently accurate to yield conclusive data. Since no assays of hormones were done on our subjects, we shall present Nathanson, Towne and Aub's data.[34]

Gonadotropic (follicle-stimulating) hormone was not found in the urine of the subjects they studied until 13 years of age, just preceding the onset of puberty. However, it probably had been present throughout pubescence but merely could not be determined by the analytic methods used. The androgens and estrogens were assayed by Oesting's colorimetric determination of 17-keto steroids and the Allen-Doisy method respectively. The results obtained by Nathanson, Towne and Aub are graphically illustrated in figure 8. These sex hormones, which are present in about equal amounts in girls and boys until just before the onset of pubescence, probably originate, according to the authors, from the adrenal cortex, but with the advent of pubescence the androgens rapidly increase in the male, paralleling the maturation of the testes. It has been our experience that the amounts of androgens

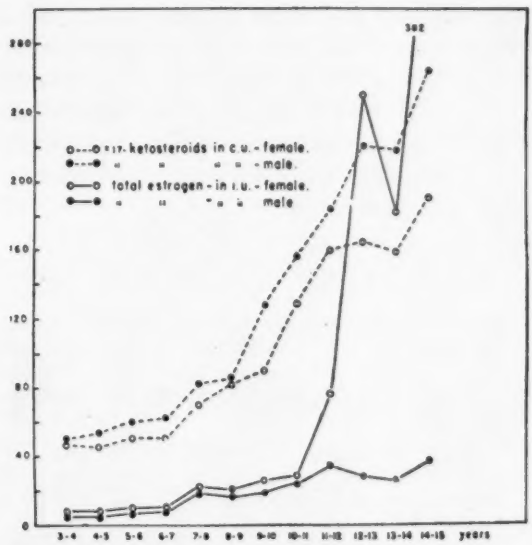

Fig. 8.—Excretion of 17-keto steroids and estrogens in prepubescence and pubescence (from Nathanson, Towne and Aub).[34]

and estrogens excreted are more closely correlated with physiologic development than with chronologic age.

Growth.—Associated with the rapid growth and development of the testes and penis of a pubescent boy there are extragenital evidences of maturity. Growth of children and pubescents has been studied in great detail by many observers; hence no attempt will be made to analyze our data as to correlation of the height and weight with pubescence.[35] It will suffice to state that about 20 per cent of the late prepubescent and early pubescent boys in this series of subjects were from 15 per cent to 50 per cent above median weight for their age. The obesity of all of these subjects was associated with normal genitalia, and many of the boys were taller than other boys of the same age.[36] It has been our observation that prepubertal

34. Nathanson, I. T.; Towne, L. E., and Aub, S. C.: Normal Excretion of Sex Hormones in Childhood, Endocrinology **28**:851, 1941.

35. Dimock, H. S.: A Research in Adolescence: Pubescence and Physical Growth, Child Development **6**:177, 1935. Greulich and others.[4a] Peter.[4b] Shuttleworth.[13c]

36. Bruch, H.: Obesity in Relation to Puberty, J. Pediat. **19**:365, 1941.

obesity [37] is a normal phenomenon in pyknic [38] or endomorphic [39] constitutional types. It is probably caused by the pronounced increase in caloric intake as a result of the ravenous appetite which so frequently develops in pubescence along with a tendency toward obesity because of the somatotype and at times because of psychogenic factors [40] with reduced exercise. Webster, Harrington and Wright [41] observed a lowered metabolic rate at this age, while others have found that during the rapid phase of development the metabolism is increased.[42] With the advent of puberty most of the boys grow taller and slimmer,[43] although Sheldon [39] has found that they maintain their characteristic biotype.

SECONDARY SEXUAL CHARACTERISTICS

(Fig. 7)

Hair Development.—The degree of development of hair is an important factor in the evaluation of the genital status even though there is a wide variation among individuals, families and races.[44] The pubic region is usually the first site where terminal hair becomes evident.[45] The first step is darkening of the villous hair at the base of the penis; the second is the extension of this growth of hair laterally toward the inguinal region, and the third is the growth upward to cover the mons pubis and adjacent portions of the lower abdominal wall in the distribution pattern of female pubic hair. In the final stage the hair extends up to the umbilicus, forming the typical male escutcheon.[46]

Axillary hair usually begins to develop after the pubic hair has passed its second stage of development, and then it becomes progressively denser. At about the

37. (*a*) Hanssen, P.: Obesity During Growth: Clinical Study, Acta med. Scandinav. **91**:435 1937. (*b*) Kornfeld, W., and Schuller, H.: Ueber Durchschnittswerte und Bewertungsgrundlagen einiger Weichteilmasse bei Kindern verschiedener Altersstufen, Ztschr. f. Kinderh. **49**:277, 1930. (*c*) Ssergeew, V. I.: Dynamick der Körperentwicklung der Jünglinge, Ztschr. f. menschl. Vererb.- u. Konstitutionslehre **19**:522, 1935.

38. Kretschmer, E.: Physique and Character, New York, Harcourt, Brace & Company, 1925.

39. Sheldon, W. H.; Stevens, S. S., and Tucker, W. B.: The Varieties of Human Physique, New York, Harper & Brothers, 1940.

40. Bruch, H., and Touraine, G.: Obesity in Childhood: The Family Frame of Obese Children, Psychosom. Med. **2**:141, 1940.

41. Webster, B.; Harrington, H., and Wright, L. M.: Standard Metabolism of Adolescence, J. Pediat. **19**:347, 1941.

42. (*a*) Nakagawa, I.: Growth and Basal Metabolism of Normal Children, Am. J. Dis. Child. **53**:991 (April) 1937. (*b*) Topper, A., and Mulier, H.: Basal Metabolsim of Normal Children; Puberty Reaction, Am. J. Dis. Child. **43**:327 (Feb.) 1932.

43. (*a*) Rosenstern, J.: Ueber die körperliche Entwicklung in der Pubertät, Ergebn. d. inn. Med. u. Kinderh. **41**:789, 1931; (*b*) Ueber die körperliche Entwicklung in der Pubertät (auf Grund von Individualuntersuchungen), Ztschr. f. Kinderh. **50**:1, 1930. (*c*) Kornfeld, W.: Ueber die Habitusentwicklung in der Pubertätszeit, Wien. klin. Wchnschr. **50**:1610, 1933. (*d*) Neurath, R.: Die Pubertät, Vienna, Julius Springer, 1932. (*e*) Schlesinger, E.: Habitus und Körperkraft bei Kindern und Jugendlichen (Ein Beitrag zum Konstitutionsproblem), Ztschr. f. Kinderh. **49**:159, 1930. (*f*) Todd, T. W.: Physical Analysis in the Adolescent Problem, Am. J. Dis. Child. **43**:533 (March) 1932. (*g*) Nobecourt, P.: Obésité et puberté, Presse méd. **46**:449, 1938.

44. Risak, E.: Ueber die verschiedenen Arten der männlichen Genitalbehaarung, Ztschr. f. d. ges. Anat. (pt. 2) **15**:164, 1930.

45. Crampton.[13d] Greulich and others.[44a]

46. (*a*) Barth, E.: Einführung in die Physiologie, Pathologie und Hygiene der menschlichen Stimme, Leipzig, G. Thieme, 1911. (*b*) Marshall, F. H. A.: Physiology of Reproduction, ed. 2, London, Longmans, Green & Co., 1922, p. 713. (*c*) Scheidt, W.: Somatoskopische und somatometrische Untersuchungen an Knaben des Pubeszenzalters, Ztschr. f. Kinderforsch. **28**:71, 1923. (*d*) Risak.[44]

same time the villous hair on the upper lip darkens and terminal hair begins to grow just inside the corners of the mouth; it gradually spreads toward the midline, with the hair becoming coarser as the process proceeds. Hair on the chin and on the sides of the face begins to grow shortly after this but usually does not become fully developed as a beard until well on in adolescence. The body and perineal hair develops long before the completion of growth of facial hair but may not reach its full development until much later.[4a, b]

One of the last secondary sex characteristics to develop is the change in hair line over the forehead, as first described by Stein.[47] The uninterrupted bowlike curve noted on immature children of both sexes changes on adolescent boys to the form found on normal men, whose curved hair line is interrupted by two wedge-shaped indentations, one over each lateral frontal region (fig. 7).

The Breast.—Although changes in the breast probably occur in nearly all boys during some stage of pubescence, they are of clinical significance in only a limited number.[48] In these boys they vary in degree from a small, painless subareolar nodule or hyperplasia of the normal mammary gland to pronounced enlargement with pain and even the presence of a colostrum-like secretion. The swelling is due to pericanalicular and periacinous infiltration with connective tissue together with epithelial hyperplasia but no true inflammatory process.

The nodules may be unilateral or bilateral. They begin to grow at varying stages of pubescence and adolescence and take varying periods of time to develop and recede. They are of no special significance unless they persist as a true gynecomastia after the genitalia have fully developed. The hyperplasia in pubescent boys is no different from that which is found in about two thirds of newborn babies.[49] In the latter it is due to the maternal and placental hormones, while in pubescent boys it is due to their own pituitary and sex hormones, the exact mechanism not being known.[50]

The Voice.—The larynx of a newborn infant is relatively large, being about one third the size of that of an adult, and in contour it is more rounded. The organ continues to grow until the third year, when a resting period begins, lasting until the onset of pubescence, during which time there seems to be no sexual distinction. During pubescence there is a rapid growth of the larynx in boys, with an associated change in its form.[51] The laryngeal cavity is enlarged and the ventrodorsal diameter considerably increased. The whole framework becomes stronger. The thyroid cartilage especially increases greatly in its dimensions, giving rise to the laryngeal prominence. The vocal folds are lengthened and thickened, the voice changing in quality and dropping about one octave in pitch.[52] These changes are for the most part effected between 14 and 18 years of age,[53] the first sign being

47. Stein, R. O.: Untersuchungen über die Ursache der Glatze, Wien. klin. Wchnschr. **1**:6, 1924.

48. Brack, E.: Ueber histologische Erscheinungen an der Mamma, speziell an den Mamillen, in der verschiedenen Lebensaltern, Arch. f. Gynäk. **122**:711, 1924. Jung, F. T., and Shafton, A. L.: Mammary Gland in the Normal Adolescent Male, Proc. Soc. Exper. Biol. & Med. **33**:455, 1935; Mastitis, Mazoplasia, Mastalgia and Gynecomastia in Normal Adolescent Males, Illinois M. J. **73**:115, 1938.

49. Lyons, W. R.: Hormonal Basis for "Witches' Milk," Proc. Soc. Exper. Biol. & Med. **37**:207, 1937.

50. Preissecker, E.: Hormonal bedingte Brustdrüsenschwellung in der Präpubertät, Zentralbl. f. Gynäk. **61**:1421, 1937.

51. Footnotes 4 *a*, 4 *b* and 46.

52. Curry, E. T.: Pitch characteristics of the Adolescent Male Voice, Speech Monog. **7**:48, 1940.

53. Fujita, T.: Medizinische Studie über den Stimmwechsel (Mutation) bei Schülern, Fukuoka acta med. **28**:105, 1935.

a break in the voice about midpubescence, the result according to Froeschels[54] of imbalance of the small cricothyroid and the larger thyrohyoid muscles.

Correlation of Primary and Secondary Sexual Characteristics (fig. 9).—Having observed in normal boys and men from birth to 25 years of age the size of the testes and penis as well as the state of development of the prostate and seminal vesicles and the degree of maturation of the secondary sexual characteristics, we have attempted to correlate these factors.[55] The boys were arbitrarily subdivided into six groups according to their genital status. In the first group were included all the prepubescent boys without any evidence of active genital growth or of

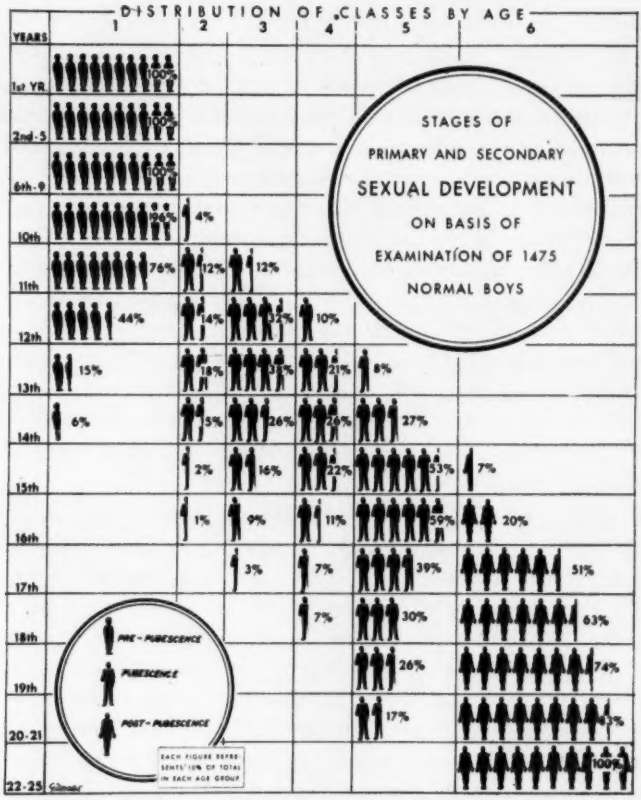

Fig. 9.—Age distribution of the various stages of primary and secondary sexual development.

secondary sexual characteristics. In the sixth group were included all the fully matured subjects, while in the second, third, fourth and fifth groups were included all the boys in the phase of pubescence. The qualifying criterion for the second stage is the beginning of active growth of the testes with some growth of penis but no pubic hair as yet. The third, fourth and fifth groups include respectively the three intervening stages of development of pubic hair with the associated enlargement of genitalia, as illustrated in figure 8.

54. Froeschels, E.: (*a*) Ueber Sprach- und Stimmstörungen der Pubertät, Fortschr. d. Med. **51**:935, 1933; (*b*) personal communications to the authors.

55. Laroche, G., and others: La puberté: Étude clinique et physiopathologique, Paris, Masson & Cie, 1938. Crampton.[13d] Kubitschek.[18]

With this classification as a basis the subjects were subdivided according to genital status at each age and the frequency distribution plotted in figure 9. This chart illustrates the variations in biologic maturity at each age, an important consideration to bear in mind in judging whether the genital status of a subject is within normal limits, because knowing the average median [56] age of onset of pubescence is of no aid in the management of the individual,[24] from the physical, the endocrinologic or the psychiatric viewpoint.

SUMMARY

A method of measuring the size of the penis and testes is described which was found to be both clinically and statistically reliable and valid. The measurements taken were the length and circumference of the fully stretched flaccid penis and the volume of each testis. The length of the penis was measured on the dorsal surface with an ordinary centimeter ruler and its circumference with a special set of gages. The volume of the testes was determined by comparing them with standard models of known volume.

Fifteen hundred normal boys and men varying in age from 1 day to 25 years were studied as to range of size of the penis and testes, size and shape of the prostate and extent of maturation of the secondary sexual characteristics; these variables were all correlated with chronologic age.

The measurements of the penis and testes are graphically presented, showing the trend of growth. During the first two years, there is only slight growth of the testes and increase in the circumference of the penis, while the length of the penis continues to grow until about 4 or 5 years of age. After this initial slight growth there is no appreciable change throughout prepubescence until the onset of pubescence, when there is a rapid spurt reaching its maximum during the postpubescent period. The variation as to the age at the pubescent spurt and the rapidity of its development is so great that there is a wide range of normal between 10 and 18 years of age. The actual measurements and their percentile distributions are charted.

The secondary sexual characteristics have been correlated with the size of the testes and penis and graphically presented by subdividing biologic maturity into six arbitrary subdivisions. The age distribution of each of these groups was also studied.

The following persons cooperated in this study: Drs. Earl T. Engle, Robert F. Loeb, Donovan J. McCune, Rustin McIntosh, Irving H. Pardee and A. Ashley Weech, of Columbia-Presbyterian Medical Center; Drs. Robert T. Frank and Béla Schick, of Mount Sinai Hospital; Dr. Louis H. Barenberg and Mrs. Alice Turck, of the social service staff of Morrisania City Hospital, and Dr. Robert L. Dickinson and the professional staff of the Schering Corporation.

171 Echo Place, New York.

56. Median, 13.17 years of age; first decile, 11.22 years of age; ninth decile, 14.76 years of age.

SYMPHALANGISM

A FAMILIAL MALFORMATION

PAUL FREUD, M.D.
AND
LAWRENCE B. SLOBODY, M.D.
NEW YORK

Symphalangism results from the failure of an interphalangeal joint to form. There may be complete or partial lack of development of the joint. When the interphalangeal joint is entirely absent, there is no dividing line between the two phalanges. Rather, they appear as a single long phalanx with a common bone marrow cavity. The trabecular structure of the bone is changed to conform to the new stresses of pull and pressure. When the interphalangeal joint has developed slightly, there are two distinct bones and two bone marrow cavities. The ligaments are shorter than normal, and there is a solid fibrous connection between the two bones. Motion is impossible. When the development of the interphalangeal joint has progressed a little further, some bending and stretching become possible.

Usually one person will exhibit the various degrees of symphalangism in different fingers. Any or all of the four extremities may be involved. The proximal interphalangeal joints are commonly involved and the distal ones only rarely. The thumbs are almost never involved and the fifth fingers infrequently. The stiffened parts of the fingers and toes have a column-like appearance, and the covering skin is smooth, with none of the folds present which are normally produced by action of the joints.

Symphalangism is familial and is often accompanied by other congenital malformations, such as syndactyly, brachydactyly, pes planus and absence of the pectoralis muscles. Thus far symphalangism has been reported [1] only in the white race. The malformation is believed

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From the Department of Pediatrics of New York Medical College, Flower and Fifth Avenue Hospitals and the Metropolitan Hospital, Department of Hospitals.

1. (*a*) Stinzing, R.: Deutsches Arch. f. klin. Med. **45**:205, 1889. (*b*) Sklodowski, J.: Virchows Arch. f. path. Anat. **121**:600, 1890 (only right hand; defect of pectoralis muscles). (*c*) Benario, J.: Berl. klin. Wchnschr. **27**:225, 1890 (combination with defect of pectoralis muscles). (*d*) Moutard-Martin, and Pissary: Bull. Soc. d'anthrop. de Paris **6**:540, 1895. (*e*) Pagenstecher, E.: Deutsche Ztschr. f. Chir. **60**:239, 1901 (on the left hand only). (*f*) Walker, G.: Bull. Johns Hopkins Hosp. **12**:239 1901 (also flat feet, first American pedigree). (*g*) Engel,

to follow a simple dominant mendelian type of hereditary transmission (Walker,[1f] Cushing,[1o] Iman,[1t] Hefner,[1s] Elkin[1v] and Stiles and Weber[1j']).

SURVEY OF THE LITERATURE

This condition has been observed repeatedly [1] and has been described under a variety of terms, such as anarthrosis, hereditary ankylosis, hereditary aplasia of joints, congenital stiffening of fingers and toes and lateral fusion of finger joints. The earliest authenticated case was that of the Count of Shrewsbury, who was killed in a battle near Bordeaux, in 1453. The count's skeleton was exhumed in 1874, and symphalangism was noted in the two index fingers. Even the statue erected in the count's memory faithfully reproduced the digital malformations. Drinkwater (1907)[1i] reported the condition in a direct

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H.: Kongenitale Ankylosen an Gelenken der Hände und Füsse, Thesis, Berlin, no. 1, Berlin, G. Schade, 1902. (*h*) Mall, F. P.: Am. J. Anat. **5**:433, 1906 (discussion of embryonic ossification time). (*i*) Drinkwater, H.: Proc. Roy. Soc. Edinburgh **28**:35, 1907 (1907 [six generations] and 1917 [cited by Rochlin[1x]]; oldest reported case: 1453). (*j*) Goerlich, M.: Beitr. z. klin. Chir. **59**:441, 1908 (combined with brachyphalangia). (*k*) Hilgenreiner, H.: Ztschr. f. orthop. Chir. **24**:23, 1909. (*l*) Fischel, J.: Anat. Hefte **40**:2, 1909. (*m*) Baumann, E.: Berl. klin. Wchnschr. **49**:457, 1911. (*n*) Drey, J.: Ztschr. f. Kinderh. **4**:553, 1912 (hypoplasia and aplasia in the same case). (*o*) Cushing, H.: Genetics **1**:90, 1916 (designation as symphalangism, pedigree of 7 generations, combination with flat feet). (*p*) Pol: Virchows Arch. f. path. Anat. **229**: 388, 1920 (monograph on malformations, discussion of etiology—combination with finger muscle defects). (*q*) Duken, J.: ibid. **233**:204, 1921 (discussion of etiology). (*r*) Brügger, J.: München. med. Wchnschr. **70**:874, 1923. (*s*) Hefner, R. A.: J. Hered. **15**:323, 1924 (cases with involvement of the joints between the first and second phalanx, flat feet). (*t*) Iman, O. L.: ibid. **15**:329, 1924 (four generations). (*u*) Lewin, P.: J. Bone & Joint Surg. **7**:630, 1925 (designation of the condition as arthrogryposis multiplex congenital). (*v*) Elkin, D. C.: Hereditary Ankylosis of Proximal Phalangeal Joints, J. A. M. A. **84**:509 (Feb. 14) 1925 (five generations). (*w*) Stecher, L.: Arch. f. klin. Chir. **134**:818, 1925 (discussion of the designation). (*x*) Rochlin, D. G.: Ztschr. f. Konstitutionslehre **13**:654, 1928. (*y*) Aschner, B., and Englemann, G.: Konstitutionspathologie in der Orthopädie, Erbbiologie des peripheren Bewegungsapparates, Berlin, Julius Springer, 1928, p. 78. (*z*) Musser, J. H.: New Orleans M. & S. J. **83**:325, 1930. (*a'*) Mosenthal, R.: Verhandl, d. deutsch. orthop. Gesellsch. **26**:66, 1931. (*b'*) Perves, J.: Rev. d'orthop. **19**:628, 1932. (*c'*) Sheldon, W.: Arch. Dis. Childhood **7**:39, 1932. (*d'*) Comby, J.: Arch. de méd. d. enf. **36**:170, 1933. (*e'*) Lange, M.: München. med. Wchnschr. **81**:894, 1934 (treatment). (*f'*) Kewesch, E. L.: Fortschr. a. d. Geb. d. Röntgenstrahlen **50**:550, 1934. (*g'*) Cole, A. J.: J. Hered. **26**:225, 1935 (inheritance of fused index finger joints transmitted by female only). (*h'*) Stolzer, M.: Les raideurs articulaires congénitales multiples, Thesis, Lausanne, 1936. (*i'*) Bloom, A. R.: Radiology **29**:166, 1937. (*j'*) Stiles, K. A., and Weber, R. A.: J. Hered. **29**:199, 1938 (six generations). (*k'*) Schwarzweller, F.: Arch. f. orthop. u. Unfall-Chir. **40**:40, 1939 (relations to aplasia of limbs). (*l'*) Glasner, J.: Arq. brasil. de cir. e ortop. **7**:338, 1939.

descendant of this Count of Shrewsbury. Benario (1890),[1e] and Sklodowski (1890)[1b] described cases of missing interphalangeal joints associated with other malformations, particularly defects of the pectoralis muscles. Walker (1901)[1f] gave a detailed description of the condition. Schulin (1879)[2] demonstrated that interphalangeal joints become differentiated at about the eighth week of fetal life. Pol (1920),[1p] Duken (1921)[1q] and Aschner and Engelmann (1928)[1y] all pointed out that in symphalangism there is complete or partial lack of this differentiation. The literature contains a number of painstaking and enlightening studies of family trees, such as those reported by Walker (1901),[1f] Hefner (1924),[1s] Iman (1924),[1t] Elkin (1925)[1v] and Stiles and Weber (1938),[1j'] in which the symphalangism has been traced from generation

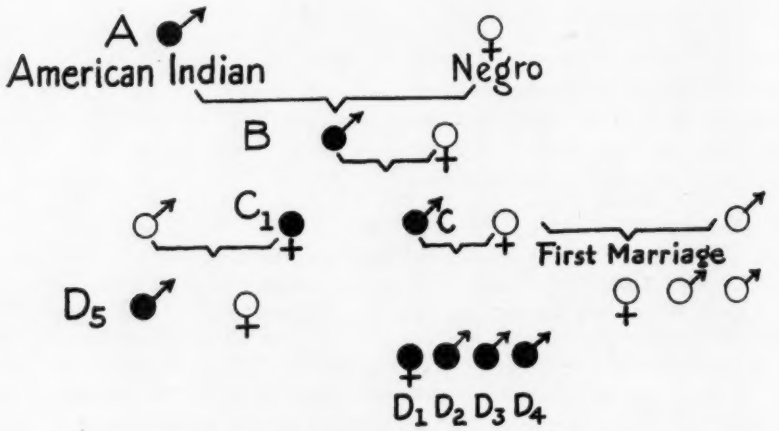

Fig. 1.—Incidence of symphalangism in four generations of a family. Black circles indicate members of the family displaying symphalangism; white circles represent members with normal joints.

to generation. Cushing (1916)[10] described an interesting family tree with 150 members; 78, or 52 per cent, of them exhibited symphalangism.

REPORT OF A FAMILY

On Oct. 2, 1941 N. B. (D_1 in figure 1), a Negro girl of 18 months with malformation of fingers and toes, was seen at the Metropolitan Hospital clinic. This otherwise healthy and normally developed child presented: (1) absence of joints between the first and second phalanges of the second, third and fourth fingers of each hand; (2) hypoplasia of the joints between the first and the second phalanx of the fifth finger of each hand; (3) aplasia of the proximal interphalangeal joints of the second, third and fourth toes of the right foot; aplasia of the proximal interphalangeal joints of the second, third and fourth toes and hypoplasia of the proximal interphalangeal joint of the fifth toe of the left foot; (4) cutaneous syn-

2. Schulin, K.: Arch. f. Anat. u. Entwcklngsgesch., 1879, p. 240.

dactyly of the proximal parts of the second and third fingers of each hand and of the fourth and fifth toes of each foot, and (5) brachydactyly, most pronounced in the thumbs and fifth fingers.

Her 3 brothers were examined and were also found to have malformation of the hands and feet.

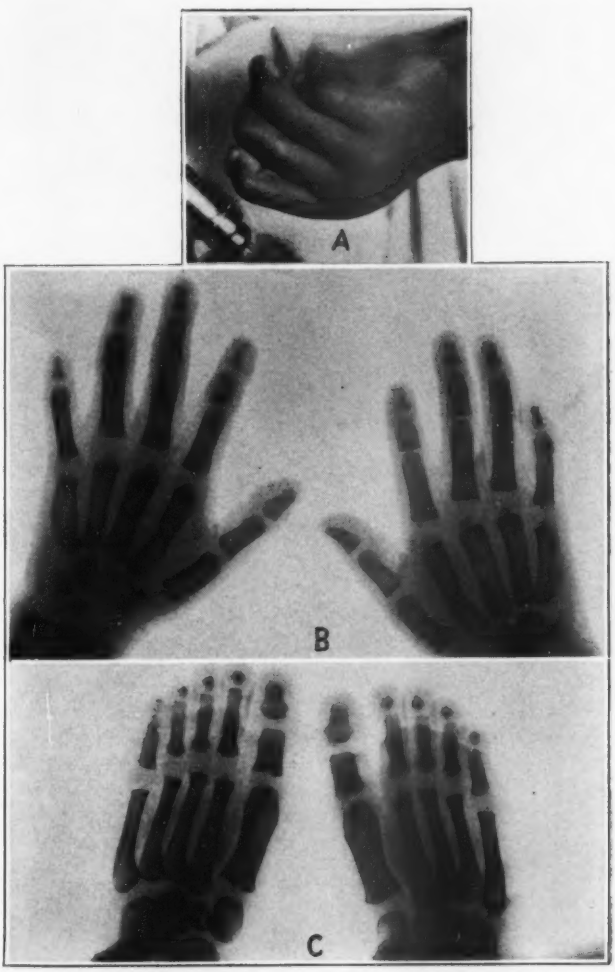

Fig. 2 N. B.(D_1).—*A*, symphalangism of the second, third and fourth fingers. *B*, increasing degrees of differentiation of the proximal interphalangeal joints from the fifth toward the second finger. *C*, complete aplasia of the proximal interphalangeal joints of all four toes.

J. B. (D_2), 3 years old, presented: (1) complete absence of the proximal interphalangeal joints of the second, third and fourth fingers of each hand; (2) hypoplasia of the proximal interphalangeal joint of each fifth finger; (3) hypoplasia of the interphalangeal joints of the third, fourth and fifth toes of each foot,

and (4) cutaneous syndactyly of the proximal parts of the second and third fingers of each hand.

W. B. (D_3), 5 years old, showed: (1) complete aplasia of the proximal interphalangeal joints of the fourth and fifth fingers of each hand; (2) complete aplasia of the proximal interphalangeal joints of the second, third, fourth and fifth

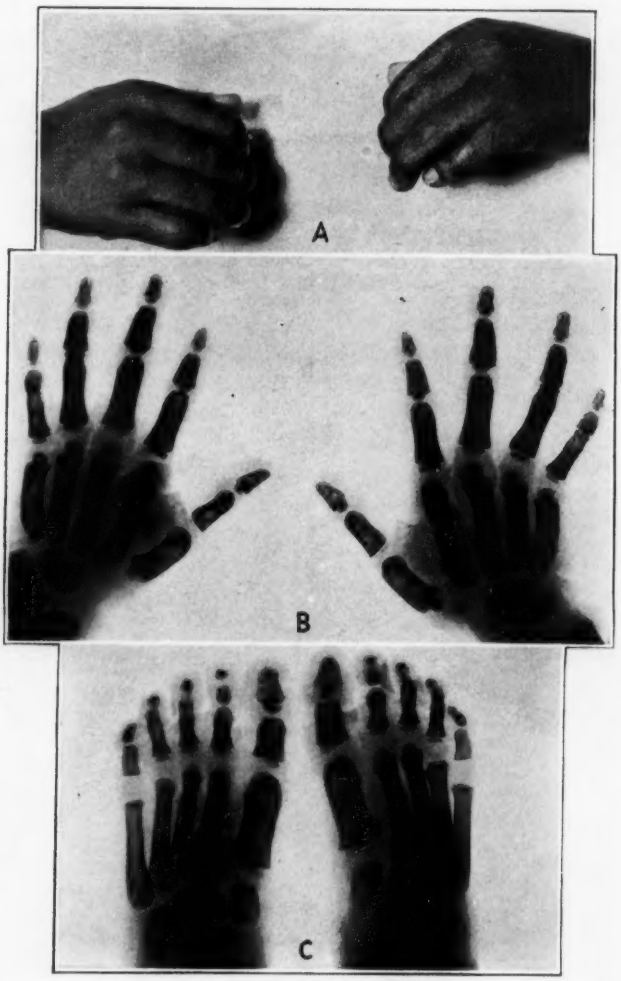

Fig. 3 J. B. (D_2).—*A* and B, symphalangism of all four fingers. *C*, symphalangism of toes.

toes of the right foot; (3) hypoplasia of the proximal interphalangeal joint of the second toe and complete aplasia of the proximal interphalangeal joints of the third, fourth and fifth toes of the left foot, and (4) cutaneous syndactyly of the proximal parts of the second and third fingers of each hand.

E. B. (D_4), 7 years old, showed: (1) complete aplasia of the interphalangeal joints of the fourth and fifth fingers and hypoplasia of these joints of the third and second fingers of each hand; (2) complete absence of the proximal interphalangeal

joints of the third and fourth toes of the right foot; complete absence of these joints of the second and third toes and partial lack on the fourth and fifth toes of the left foot, and (3) cutaneous syndactyly between the second and the third toe on each foot.

Flat feet were noted in all 4 children. Otherwise the results of the physical examinations were essentially normal.

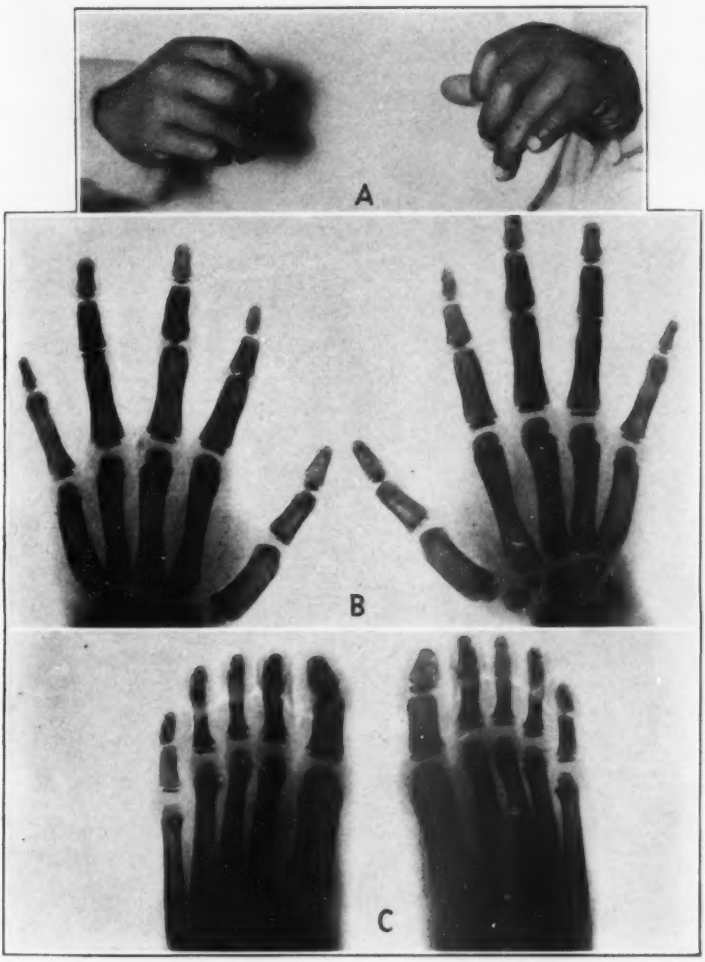

Fig. 4 W. B. (D_3).—*A*, symphalangism of fourth and fifth fingers. *B*, aplasia and hypoplasia of the interphalangeal joints of the hands. *C*, aplasia of the interphalangeal joints of the toes.

The roentgenograms of E. B. may be considered typical of all 4 children (fig. 5); the fifth fingers show a fusion of the proximal and middle phalanges. A slight constriction at the point of fusion is noted. The fourth fingers show the development of a joint space between the proximal and the middle phalanx. There is central bony bridging. This bridging is less evident in the third fingers

and almost invisible in the second fingers. The thumbs show a normal joint space. The trabeculae are accentuated in all the metacarpal bones and the phalanges. There is a zone of increased density in the distal end of each proximal phalanx. The first and fifth metacarpal bones show the presence of moderate bowing, with the concavity mesially.

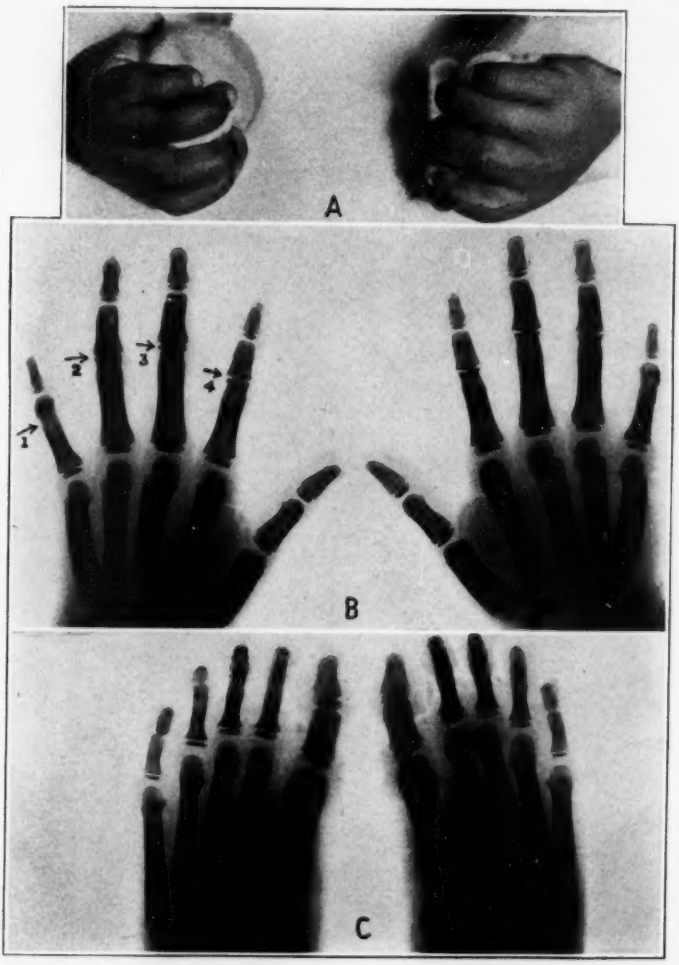

Fig. 5 E. B. (D_4).—*A*, varying degrees of symphalangism. *B*, stages of articular differentiation: (1) bony constriction; (2) incipient bridging; (3) decreased bridging; (4) disappearance of bony ridge and normal joint (epiphysial line not visible). *C*, symphalangism of toes.

The mother of N. B. (D_3) was found to be perfectly normal, and she had 3 children by a previous marriage who had no digital abnormalities. N. B.'s father (*C* in the chart), a Negro of 45 years, presented typical symphalangism. N. B.'s paternal aunt (C_1) and 1 of her aunt's 2 children (D_5) showed symphalangism. N. B.'s father (*C*) stated that his father (*B*) and his grandfather (*A*) had this

"same trouble with their fingers." The grandfather (*A*) was an American Indian who married a Negress. *B* and *C* married Negresses. N. B.'s father (*C*) knew of no other living relatives.

COMMENT

This family tree covers four generations. Nine of 10 members of the family were known to have symphalangism. The dominant character of the inherited malformation is thus illustrated. However, this 90 per cent incidence is much higher than the average figure, approximately 50 per cent, for other reported family trees. All previously reported examples of the condition have been in the white race. Although this family at first glance was thought to be Negro, it should be emphasized that one of the progenitors was an American Indian.

The malformation usually causes little inconvenience. However, among the persons observed by us the afflicted adults were severely hampered, to the point of being unable to grasp objects with one hand. In some persons the immobility of the proximal joint is compensated for by hypermobility of the distal joint.

The differential diagnosis between ankylosis of the finger joint and symphalangism is simple. Symphalangism is present from birth. Several fingers are involved; the segment is extended, and the proximal joints are usually involved. Ankylosis is acquired; the segment is usually flexed, and the distal joints are involved. Roentgen examination will make the final diagnosis if necessary.

Clinically it is often impossible to distinguish a complete aplasia of the joint from a severe hypoplasia. The finger may appear absolutely stiff, and yet on roentgen examination there may be some differentiation of the interphalangeal joint.

It should be emphasized that symphalangism is due to failure of differentiation of an interphalangeal joint during the embryonic stage. The previously held theory, that ossification of existing joints takes place in the fetus, is untenable. The roentgenograms demonstrate the stages of articular differentiation. The earliest change is a constriction of the phalangeal beam. This progresses until only a central bony bridge remains. This bridging becomes less distinct and then invisible, and then a normal joint space is formed. The process may be stopped at any point before complete differentiation, with resulting symphalangism.

SUMMARY

Symphalangism is a hereditary aplasia or hypoplasia of the interphalangeal joints. This malformation follows a simple dominant mendelian type of transmission. A representative family tree is presented in detail. The roentgenograms demonstrate the manner in which the various stages of articular differentiation occur during the life of the embryo.

OUTPUT OF BILE PIGMENT BY NEWBORN INFANTS AND BY OLDER INFANTS AND CHILDREN

LIEUTENANT RUSSELL J. TAT
AND
LIEUTENANT TIBOR J. GREENWALT
MEDICAL CORPS, ARMY OF THE UNITED STATES
AND
WILLIAM DAMESHEK, M.D.
BOSTON

In the diagnosis and follow-up of various hematologic and hepatic disorders, determinations of the fecal and urinary outputs of urobilinogen have often proved invaluable. In our own investigations this has been particularly true in the study of the hemolytic syndromes and in the differential diagnosis of hemolytic conditions from hepatic.[1] Although our study was at first largely confined to adults, the investigations which are the subject of this report have shown that these determinations are equally valuable in infancy and in childhood.

Determinations of the bile pigments in the stools of infants and of children have only occasionally been performed. This is particularly true in the case of the fecal urobilinogen. Estimations of the bilirubin output have been more frequent, but the actual time of the disappearance of bilirubin from the newborn infant's stool has been but little studied. In most communications, little or no attention has been paid to the "hemolytic index," which is the calculated relationship of pigment to the total circulating mass of hemoglobin. The present study was undertaken to remedy some of these deficiencies, especially since the establishment of normal values appeared important.

HISTORICAL SURVEY

Jaffé [2] in 1869 described a pigment which he found in both bile and urine and which he called urobilin. In freshly passed urine he also found a chromogen which was converted to urobilin on standing in an open vessel. In 1878 von Disqué called this chromogen urobilinogen. Both Jaffé and Vanlair and Masius [3] in 1871 described the presence of urobilin in normal stools. In the same year Maly produced urobilin from bilirubin by reduction with sodium amalgam. In 1893

From the Blood Laboratory of the Boston Dispensary, the Boston Floating Hospital, and the J. H. Pratt Diagnostic Hospital; aided by grants from the Charlton Fund, Tufts College Medical School, and Mead Johnson and Company.

1. (*a*) Singer, K.; Miller, E. B., and Dameshek, W.: Hematologic Changes Following Splenectomy in Man with Particular Reference to Target Cells, Hemolytic Index and Lysolecithin, Am. J. M. Sc. **202**:177-187, 1941. (*b*) Singer, K., and Miller, E. B.: Studies in Urobilinogen, Bull. New England M. Center **2**:302-305, 1940. (*c*) Dameshek, W., and Singer, K.: Familial Non-Hemolytic Jaundice, Arch. Int. Med. **67**:259-285 (Feb.) 1941. (*d*) Miller, E. B.; Singer, K., and Dameshek, W.: Use of the Daily Fecal Output of Urobilinogen and the Hemolytic Index in the Management of Hemolysis, ibid. **70**:722-737 (Nov.) 1942. (*e*) Watson, C. J.: Studies on Urobilinogen: The Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Disease of the Liver, ibid. **59**:206-231 (Feb.) 1937.

2. Jaffé, M.: Zur Lehre von Eigenschaften und der Abstammung der Harn Pigmente, Virchows Arch. f. path. Anat. **47**:405-427, 1869.

3. (*a*) Cited by Watson;[1d] (*b*) cited by Schmidt and Strasburger.[5d]

von Müller [4] originated the theory of the enterogenous formation of urobilin, basing his conclusions on the absence of urobilin from the stools and urine of newborn infants and from those of a patient with complete obstruction of the common bile duct. When the latter was fed urobilin-free hog bile, urobilin was demonstrated in the stool two days later and thereafter in the urine.

Although Ehrlich described his paradimethylaminobenzaldehyde reaction in 1890 [4a] it was not until 1903 that Neubauer [4b] showed that it was due to urobilinogen.

It has long been known that bilirubin and biliverdin are the predominating bile pigments in the stools of newborn infants.[5] Much controversy has arisen regarding the time of appearance of urobilin in the infant's stool. Von Müller [6] was unable to find urobilin until the third day of life. Schorlemmer [5c] found it in the stools of artificially fed infants on the seventh day and in those of breast-fed infants on the fourteenth to fifteenth day. Although Denzer and Merritt [7] found it as early as the second week of life, Lucas [8] and co-workers failed to find it before the tenth week. Marheineke [9] felt that the presence of urobilin in the feces before the first month of life was evidence of hepatic damage. Although Meyer and Adler [10] found urobilin in both urine and feces of most newborn infants, they considered it a sign of hepatic dysfunction. Ross, Waugh and Malloy [11] agreed with Snelling's [12] observations, that urobilin appears in the stool at about the third or fourth day of life. Passini [13] found urobilin in the meconium of one fourth of a large series of newborn infants. He believed that it originated by transfer of pigment through the placenta, especially since Lemaire [14] had demonstrated its presence in the cord blood. Bang [15] failed to find urobilin in the meconium regularly.

Little work has been done on the disappearance time of bilirubin from the infant's stool. Although Giaume and Lanza [16] stated that the pigment usually disappears about the seventh month of life, they observed cases in which it was no longer

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4. von Müller, F.: Ueber Icterus, Jahresb. d. schles. Gesellsch. f. väterl. Kult (med. Sekt.) **70**:1-13, 1893.

4a. Cited by Bang.[15]

4b. Neubauer, O.: Ueber die Beudeutung der neuen Ehrlichschen Farbenreaktion (mit Dimethylaminobenzolaldehyde), München. med. Wchnschr. **50**:1846, 1903.

5. (*a*) Simon, J. F.: Analysen animalischer Substanzen in Flüssigkeiten, Arch. d. Pharm. **22**:35, 1840. (*b*) Zweifel, P.: Untersuchungen über das Meconium, Arch. f. Gynäk. **7**:474-490, 1875. (*c*) Schorlemmer, R.: Ueber den Nachweis von Gallenfarbstoff in den Faeces, insonderheit mit der Ad. Schmidt'schen Probe, und über die klinische Bedeutung des Vorkommens von Bilirubin in denselben, Arch. f. Verdauungskr. **6**:263-284, 1900. (*d*) Schmidt, A., and Strasburger, J.: Die Fäzes des Menschen, ed. 4, Berlin, August Hirschwald, 1915, pp. 268-281.

6. von Müller, cited by Schmidt and Strasburger.[5d]

7. Denzer, B. S., and Merritt, K. K.: Studies on Anemia in Infancy: The Urobilin Content of the Stools of Normal Infants, Am. J. Dis. Child. **27**:297-302 (April) 1924.

8. Lucas, W. P.; Dearning, B. F.; Hoobler, H. R.; Cox, A.; James, M. R., and Smith, F. S.: Blood Studies in the Newborn, Am. J. Dis. Child. **22**:525-559 (Dec.) 1921.

9. Marheineke, K.: Ueber das Auftreten von Urobilin im Stuhl von Neugeborenen und Säuglingen, Jahrb. f. Kinderh. **108**:326-336, 1925.

10. (*a*) Meyer, E., and Adler, A.: Ueber den Bilirubinstoffwechsel bei Neugeborenen, Zentralbl. f. Gynäk. **28**:1514-1520, 1924. (*b*) Goldschmidt-Schulhoff, L., and Adler, A.: Ueber das Vorkommen von Urobilin im Stuhl und Harn von Neugeborenen, ibid. **28**:1520-1531, 1924.

11. Ross, S. G.; Waugh, T. R., and Malloy, H. T.: The Metabolism and Excretion of Bile Pigment in Icterus Neonatorum, J. Pediat. **11**:397-408, 1937.

12. Snelling, C. E.: Icterus Neonatorum, J. Pediat. **2**:399-413, 1933.

13. Passini, F.: Urobilin im Mekonium, Ztschr. f. Kinderh. **53**:175-180, 1932.

14. Lemaire, cited by Passini.[13]

15. Bang, O.: Klinische Urobilinstudien, Acta med. Scandinav. (supp.) **29**:1-203, 1929.

16. Giaume, C., and Lanza, P.: Determinazione quantitativa della bilirubina nel meconio e nelle feci del lattante, Pediatria **37**:519-537, 1929.

found in the third month and others in which it was present as late as the fourteenth month. Ylppö [17] demonstrated bilirubin in the stools of 2 infants as late as 2½ months, while Dordi and Rossi [18] found a trace of bilirubin in the stool of a 7 month old infant and no bilirubin in the stool of another infant 8 months of age.

Jaffé [2] originally discovered urobilin by noting its fluorescence in urines treated with zinc salts; he also described its characteristic absorption spectrum. These properties of urobilin as described by Jaffé have been the basis for many methods for its determination, although it may be stated that the large number of methods is in itself evidence of their inadequacies. In 1914 Wilbur and Addis [19] gave a complete review of quantitative methods for the determination of urobilin. In 1925 Terwen [20] published a new method based on the complete reduction of urobilin to urobilinogen and utilization of Ehrlich's aldehyde reaction for colorimetric determination.

The quantitative determination of the fecal excretion of bilirubin and urobilinogen in the newborn period has only occasionally been reported (table 1).

TABLE 1.—*Excretion of Bile Pigments by Normal Infants*

Author	Period of Life	Fecal Bilirubin, Mg./Day		Fecal Urobilin, Mg./Day	
		Range	Average	Range	Average
Ylppö	1-5 days	.....	6.79	Not determined	
	6-8 days	.....	11.86		
	9-11 days	.....	9.53		
	12-13 days	.....	14.13		
Giaume and Lanza	Newborn (meconium only)	7.04-24.67	13.88	Not determined	
Kerppola and Leikola	Newborn (meconium only)	3.0-58.8	27.38	Not determined	
Snelling	1-3 days	Not determined		.....	None
	4th day			.....	0.65
	5-16 days			2.66-5.21	3.7
Dordi and Rossi	10th day	5.41	.....	3.44	....
	10th day	4.78	.....	3.73	....
Ross, Waugh and Malloy	1-2 days	48.2-57.5	52.9	.....	None
	3-5 days	21.1-27.3	23.2	33.5-44.4	38.4
	6-7 days	11.5-16.8	14.2	57.7-69.3	63.5
Present authors	1-5 days	1.0-23.0	8.6	Trace to 0.70	....
	5-10 days	0.0-16.0	5.7		
	10-15 days	0.3-12.4	5.3		

Ylppö [17] in 1913, utilizing a quantitative spectrophotometric technic, studied the excretion of bilirubin with special reference to jaundice of the newborn. The values in his series of cases (table 1) average 6.79 to 14.13 mg. per day.

In 1929 Giaume and Lanza,[16] employing Zamorani's diazo method for fecal bilirubin, found 7.04 to 24.67 mg. per day in the meconium of 7 newborn infants (table 1). Zamorani's method is a modification of van den Bergh's test for serum bilirubin applied to alcoholic extracts of stools.

Kerppola and Leikola [21] (1932) performed determinations of bilirubin on five specimens of meconium, using Ehrlich's diazo reaction on acidified chloroform extracts. Their results ranged from 3 to 58.8 mg. per day (table 1).

17. Ylppö, A.: Icterus neonatorum und Gallenfarbstoffsekretion beim Fötus und Neugeborenen, Ztschr. f. Kinderh. **9**:208-318, 1913.

18. Dordi, A. M., and Rossi, G.: Sul ricambio emoglobinico nel lattante e nel bambino normale, Riv. di clin. pediat. **34**:594-600, 1936.

19. Wilbur, R. L., and Addis, T.: Urobilin: Its Clinical Significance, Arch. Int. Med. **13**:235-286 (Feb.) 1914.

20. Terwen, A. J. L.: Ueber ein neues Verfahren zur quantitativen Urobilinbestimmung in Harn und Stuhl und über die Bereitung und die Eigenschaften von einem möglichst reinen Urobilinpräparat, Deutsches Arch. f. klin. Med. **149**:72-101, 1925.

21. Kerppola, W., and Leikola, E.: Zur Chemie des Bilirubins, Acta med. Scandinav. **78**: 24-41, 1932.

In 1933 Snelling [12] studied the excretion of urobilinogen, using the method of Elman and McMaster.[22] With this method the fluorescence produced by urobilin with a reagent of alcoholic zinc acetate is compared with the fluorescence of a dilute solution of acroflavine. The bilirubin content of the stools was estimated from the width of the corresponding spectral absorption band. In the first three days of life, no urobilin was found and only occasionally was bilirubin demonstrated. After this period, two groups of infants could be discriminated, one excreting only urobilin and the other bilirubin, although an occasional baby had both in its feces. These observations are at variance with our results. Snelling found no urobilin during the first three days of life, 0.65 mg. on the fourth day and an average value of 3.7 mg. for the fifth to sixteenth day period (table 1).

In 1936 Dordi and Rossi [18] utilized Zamorani's method for bilirubin and Terwen's method for urobilinogen in studying a group of children. In the feces of 2 infants 10 days of age, they found 5.41 and 4.78 mg. per day of bilirubin and 3.44 and 3.73 mg. per day of urobilinogen respectively (table 1).

In 1937 Ross, Waugh and Malloy [11] studied the fecal urobilin and bilirubin excretion of normal and of jaundiced babies. They determined urobilin by a modification of Joseph's method, which closely resembles the method of Elman and McMaster. The bilirubin was determined by a modification of Hooper and Whipple's [23] method adapted to the Evelyn photoelectric colorimeter. This procedure utilizes a solution of 2 cc. of concentrated nitric acid, 10 cc. of concentrated hydrochloric acid and sufficient alcohol to make 500 cc. The reagent oxidizes bilirubin and its derivatives to bilicyanin, and the resulting color is determined in a suitable colorimeter. The results of Ross, Waugh and Malloy (table 1) ranged from 11.5 to 57.5 mg. of bilirubin per day and from 0 to 69.3 mg. of urobilin per day for the first week of life.

Few studies have been made of the fecal excretion of urobilinogen of normal children past infancy. In 1924 Denzer and Merritt [7] studied a group of normal infants under 1 year of age, employing the method of Wilbur and Addis.[19] Their figures ranged from 0 to 119 "dilution units" per day. Bass, Denzer and Herman [24] found values which did not exceed 800 "dilution units" for children 6 years of age and up to 1,400 units for children up to 11 years, using the same method. Merritt [25] found somewhat lower values for this older group. Wilbur and Addis' normal values for adults were 3,307 to 8,737 "dilution units" per day. Opitz and Choremis [26] (1927), using a modification of Adler's fluorometric method, found 1.24 to 7.1 mg. of urobilinogen per day in the feces of 3 children under 1 year of age and 21.6 to 50.0 mg. per day in those of 5 children from 3½ to 12 years of age. Josephs[27] in 1934, also employing a fluorometric method, obtained values of 13.0 to 30.0 mg. per day for normal children under 1 year of age and 22 to 88 mg. per day for children from 1 to 12 years of age. He found that the hemolytic

22. Elman, R., and McMaster, P. D.: Studies on Urobilin Physiology and Pathology: I. The Quantitative Determination of Urobilin, J. Exper. Med. **41**:503-512, 1925.

23. Hooper, C. W., and Whipple, G. H.: Bile Pigment Metabolism: I. Bile Pigment Output and Diet Studies, Am. J. Physiol. **40**:332-349, 1916.

24. Bass, M. H.; Denzer, B. S., and Herman, H.: Urobilin Excretion in the Anemias of Infants and Children, Am. J. Dis. Child. **27**:433-437 (May) 1924.

25. Merritt, K. K.: Urobilin Excretion in Children with Anemia, Am. J. Dis. Child. **30**:667-669 (Nov.) 1925.

26. Opitz, H., and Choremis, K.: Untersuchungen über den Urobilin-Stoffwechsel bei Kindern insbesondere nach Bluttransfusionen und in Tierversuch, Jahrb. f. Kinderh. **115**:23-67, 1927.

27. Josephs, H. W.: Urobilin Excretion of Infancy and Childhood: Relation to Blood Destruction and Formation, Bull. Johns Hopkins Hosp. **55**:154-167, 1934.

index, which ranged from 52 to 78 in the second month of life, decreased progressively with age until it reached the adult level, of about 20, at 8 to 12 years of age. In 1936 Dordi and Rossi,[18] in addition to their studies on bilirubin, determined the fecal output of urobilinogen of a group of children up to 7 years of age with use of Terwen's method. For the group under 2 years of age, their highest value was 5.91 mg. of urobilinogen per day. After the second year, the values ranged from 8.1 to 47.5 mg. per day. These authors devised a hemolytic index with unity as the normal figure for adults. In general, they concluded that for children under 3 years of age the hemolytic index is lower than that for adults whereas for those over 3 years of age the hemolytic index is higher. In 1938 Simon,[28] using the spectrophotometric method of Heilmeyer and Krebs,[29] studied a group of 9 children from 4 to 11 years of age. He found that the fecal excretion of urobilinogen of this group did not exceed 20 mg. per day and that the average daily excretion was 7.8 mg.

EXPERIMENTAL PROCEDURE

Methods.—Fecal Bilirubin: The method of Malloy and Evelyn[30] was used. Individual stools were wrapped in waxed paper shortly after passage and placed in a waxed cardboard container. Specimens collected over a period ranging from three to six days were pooled by thorough mixing in a waxed cardboard container. A 10 Gm. sample, or the entire collection if small, was then thoroughly ground with 290 cc. of distilled water in a mortar until a homogeneous suspension resulted. To 10 cc. of this fine suspension (the remainder was used for the determination of fecal urobilinogen) were then added 15 cc. of 95 per cent ethyl alcohol and 25 cc. of Malloy and Evelyn's reagent (0.4 cc. of 30 per cent hydrogen peroxide and 2 cc. of concentrated hydrochloride acid in 100 cc. of 95 per cent ethyl alcohol). This mixture was put in a large test tube, which was stoppered and allowed to stand for one hour at room temperature without any protection from light and with occasional agitation to insure thorough mixing and oxidation. A portion of the mixture was then centrifuged at high speed (or filtered) until crystal clear, and the supernatant solution (or filtrate) was read in a Cenco photelometer with a no. 4 red filter and 95 per cent ethyl alcohol as the blank. Although two extractions are recommended by Malloy and Evelyn, a single extraction was employed in this study, since it was found that little additional color developed on the second extraction. The photelometer readings were converted into values for bilirubin with use of a curve constructed from previous determinations on known solutions of chemically pure bilirubin (Eastman Kodak Co.).

This method, which is an oxidation procedure, has the advantage over the diazo method (van den Bergh) in that it measures both bilirubin and biliverdin, while the diazo reaction is specific for bilirubin alone.

The Malloy and Evelyn procedure is admittedly not a perfect method for the determination of fecal bilirubin, since it is based on a somewhat unreliable color reaction which makes extreme accuracy unattainable. However, we have tested the constancy of the method by daily serial determinations for as long as seven days on the same stool specimen in both the emulsified and the solid state and have noted no significant variation in the results. The amount of bilirubin in a freshly passed stool has also been found to remain constant after several days in a waxed cardboard container. Recovery experiments have been unsatisfactory, owing to difficulty in completely mixing the bilirubin with the stools. Our control experiments indicate that the method used is applicable to such comparative studies as we have made in this and a subsequent investigation.

Fecal Urobilinogen: Quantitative determinations were made by the method of Watson,[31] which is based on the original method of Terwen[20] and the modification of Fürth and

28. Simon, K. T.: Ueber die Urobilin- und Stercobilinausscheidung des lebergesunden Kindes vor und nach Decholingaben, Jahrb. f. Kinderh. **152**:338-347, 1938-1939.

29. Heilmeyer, L., and Krebs, W.: Die quantitative Bestimmung des Urobilins und Urobilinogens mit dem Zeisschen Stufenphotometer, Biochem. Ztschr. **231**:393-398, 1931.

30. Malloy, H. T., and Evelyn, K.: Oxidation Method for Bilirubin Determinations in Bile and Meconium with Photoelectric Colorimeter, J. Biol. Chem. **122**:597-603, 1938.

31. Watson, C. J.: The Average Daily Elimination of Urobilinogen in Health and in Disease, with Special Reference to Pernicious Anemia, Arch. Int. Med. **47**:693-726 (May)

Singer.[32] The total stools for four days (sometimes for as long as six days in the case of infants) were collected in water-proof waxed cardboard ice cream containers with tight-fitting covers. After thorough mixing of the whole specimen a 10 Gm. sample was thoroughly emulsified with 290 cc. of distilled water, either with a mortar and pestle or with a mechanical mixing device. This emulsion was then mixed with 100 cc. of 20 per cent ferrous sulfate (freshly prepared) in a large Erlenmeyer flask. To this was added slowly and with thorough shaking 100 cc. of 10 per cent sodium hydroxide. The flask was stoppered and placed in the dark. After one hour, the mixture was filtered and 10 cc. of filtrate (or an appropriate amount) was removed. This was added to 3 cc. of glacial acetic acid and 40 cc. of distilled water in a separatory funnel. Complete extraction with 40 cc. of purified petroleum benzene (petroleum ether) was then carried out; the aqueous layer was discarded, and the petroleum benzene layer was then washed twice with distilled water and the water layer discarded. The petroleum benzene layer was then shaken with 2 cc. of Ehrlich's aldehyde reagent and the colored layer separated after the addition of 3 cc. of saturated solution of sodium acetate and further shaking. The extraction with Ehrlich's reagent and sodium acetate was repeated until no further color developed. The total volume of final colored solution thus obtained was measured and the color read in a phenolsulfonphthalein colorimeter (Hellige). Calculation was then carried out as recommended by Watson.

Watson's method has been in use in our laboratory for several years, and we have found it reliable and simple and not requiring expensive or specialized equipment. Older methods for the determination of urobilinogen, and even some of those still in use, require not only specialized apparatus but a great deal of experience and thus do not lend themselves so readily to routine laboratory practice as does Watson's method.

Urinary Urobilinogen: Twenty-four hour specimens of urine were collected under purified petroleum benzene (petroleum ether) in a stoppered brown bottle into which 5 Gm. of anhydrous sodium carbonate (chemically pure) had been put. The urinary urobilinogen was determined quantitatively by the method of Watson.[31]

Blood Volume: Figures for the volume of blood were calculated from the data of Brines, Gibson and Kunkel,[33] who studied the blood volumes of infants and of children by the Evans blue dye method.

Hemolytic Index: The formula of Belonogowa[34] for determination of the hemolytic index was employed:

$$\frac{\text{Total daily urobilinogen or bilirubin in milligrams} \times 100}{\text{Total circulating hemoglobin in grams}}$$

This expresses the number of milligrams of bile pigment excreted per day per hundred grams of circulating hemoglobin. We have used values for bilirubin and for urobilinogen interchangeably because these substances differ so little in molecular weight that it is not necessary to distinguish between them in applying this formula.

Results.—Determinations of fecal bilirubin and urobilinogen were made on a series of 30 normal newborn infants to establish normal values (table 1). From the first to the fifth day of life the values for bilirubin ranged from 1 to 23 mg. per day, with an average excretion of 8.6 mg.; in the next five day period the range was 0 to 16 mg. per day, with an average excretion of 5.7 mg., and from the tenth to the fifteenth day the range was 0.3 to 12.4 mg. per day, with an average excretion of 5.3 mg. The values for fecal urobilinogen for these babies ranged from a trace to 0.70 mg. per day. The hemolytic indexes (table 2) of 8 of these newborn infants for whom the necessary data were obtained ranged from 0.5 to 29.7 during the period covering the fifth through the eleventh day of life. A comparison between our figures and those of other workers is shown in table 1.

1931; Studies of Urobilinogen: I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**:458-475, 1936; Studies of Urobilinogen: II. Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, Arch. Int. Med. **59**:196-206 (Feb.) 1937.

32. Singer, K.: Studium zum Problem der Blutmauserung: Ueber den Einfluss der Ernährung auf die Urobilinogenausscheidung mit den Fäzes, Wien. Arch. f. inn. Med. **20**: 59-80, 1930.

33. Brines, J. K.; Gibson, J. G., Jr., and Kunkel, P.: The Blood Volume in Normal Infants and Children, J. Pediat. **18**:447-457, 1941.

34. Belonogowa, N. S.: Ueber den Blutumsatz bei verschiedenen Anämien und die Beeinflussung desselben durch die Behandlung mit Bluttransfusion, Salvarsan, Arsen, Eisen und Leberdiät, Deutsches Arch. f. klin. Med. **192**:297-329, 1928.

In order to determine the age at which bilirubin disappears from the infant's stool, we studied a group of 6 normal newborn infants continuously from birth. The results (table 3) show that in the feces of 2 infants (babies Gin. and Pub.) bilirubin could not be demonstrated after the eighth and the tenth day respectively. In the stools of the remaining 4 infants (Haf., Cha., Cas. and Mey.) bilirubin was present in small amounts at the end of the period of study, which was fifty-four, sixty-four, sixty-five and seventy-five days respectively. The determinations for these infants, however, showed wide fluctuation in the amount of bilirubin, and on several occasions the pigment disappeared, only to reappear in a subse-

TABLE 2.—*Excretion of Pigments in the Stools and the Hemolytic Index of Normal Newborn Infants*

Infant	Day of Life	Red Blood Cells, Millions	Hemoglobin, Gm.	Total Stool Pigment, Mg./Day	Hemolytic Index *
1	10	6.38	19.4	8.8	15.1
2	7	6.90	22.9	8.6	12.5
3	5	6.35	21.9	19.5	29.7
4	10	6.37	20.8	1.6	2.6
5	9	6.87	20.4	2.3	3.7
6	8	5.43	16.5	0.3	0.5
7	11	6.06	20.8	3.8	6.1
8	11	5.92	18.1	3.8	7.0

* Blood volume of 300 cc. used in calculation.

TABLE 3.—*Disappearance Time of Fecal Bilirubin in Normal Infants*

Baby	Day of Life	Fecal Bilirubin, Mg./Day	Fecal Urobilinogen, Mg./Day	Baby	Day of Life	Fecal Bilirubin, Mg./Day	Fecal Urobilinogen, Mg./Day
Pub.	1-6	6.6	0.3	Cha.	1-5	3.7	None
	6-9	1.8	Trace		5-9	12.9	None
	9-10	....	...		9-12	20.5	None
	10-15	None	0.8		12-16	9.2	Trace
Mey.	1-7	11.7	Trace		16-20	17.2	0.3
	7-12	1.7	Trace		20-26	11.7	0.3
	12-17	2.9	Trace		26-31	13.9	0.7
	17-21	....	.....		31-35	None	0.2
	21-24	6.8	Trace		35-42	12.5	0.3
	24-30	1.2	Trace		42-45	....	...
	30-36	1.0	Trace		45-48	None	...
	36-42	2.6	Trace		48-55	None	Trace
	42-46	6.2	0.2		55-64	15.7	0.3
	46-56	2.7	Trace	Gin.	1-3	9.5	None
	56-60	None	.....		3-8	None	0.7
	60-67	Trace	0.4		8-15	....	...
	67-75	1.2	Trace		15-18	None	0.5
Cas.	1-7	2.0	Trace				
	7-11	12.5	Trace	Haf.	1-6	2.3	None
	11-14	7.2	None		6-10	1.3	Trace
	14-17	9.5	None		10-18	...	.....
	17-22	2.9	None		18-22	0.7	None
	22-28	8.6	None		22-28	None	Trace
	28-33	5.5	Trace		28-35	0.8	Trace
	33-37	7.2	None		35-40	0.8	Trace
	37-44	2.5	None		40-48	Trace	Trace
	44-49	3.1	None		48-54	1.1	Trace
	49-57	1.9	None				
	57-65	0.9	None				

quent collection. Thus, no accurate statement can be made as to the exact time of disappearance of bilirubin from a newborn infant's stool.

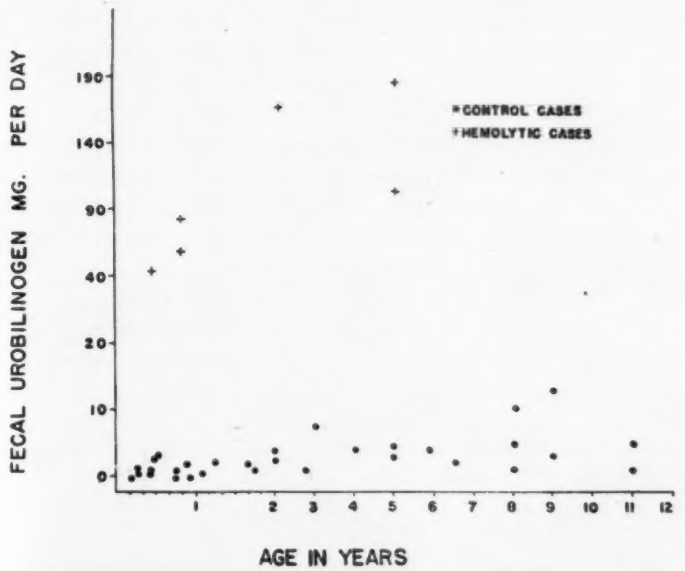
Urobilinogen was demonstrable in traces in the feces of these 6 infants and of all except 1 of the series of 30 normal newborn infants within the first week of life. Since only pooled specimens of several days were studied, a more accurate statement cannot be made.

To establish normal values for fecal excretion of urobilinogen of children, we studied a group of 31 children hospitalized for various reasons. Children who had hemolytic anemia or hepatic or biliary disease or who received any form of therapy with one of the sulfonamide compounds were excluded. From children with an acute illness collections were made only during convalescence.

The data for these children are recorded in table 4 and in the accompanying chart. Although no definite correlation can be drawn between the figures for fecal excretion of urobilinogen and the children's age and the total mass of circulating hemoglobin, it can be

TABLE 4.—*Fecal Excretion of Urobilinogen and Hemolytic Indexes of Control Patients*

	Patient	Age	Diagnosis	Weight, Kg.	Red Blood Cells, Millions	Hemoglobin, Gm.	Blood Volume, Cc.	Fecal Urobilinogen, Mg./Day	Hemolytic Index
1	W. S.	2 mo.	Malnutrition	2.8	4.05	12.5	300	None	...
2	J. D.	3 mo.	Malnutrition	4.5	4.00	13.1	300	Trace	...
3	B. B.	3 mo.	Malnutrition	3.4	3.95	12.5	300	1.1	2.9
4	F. F.	5 mo.	Gastroenteritis	6.8	4.03	12.5	400	Trace	...
5	P. S.	5 mo.	Congenital heart disease	2.7	4.00	11.0	300	0.5	1.5
6	M. B.	5½ mo.	Convulsions ?	7.9	4.10	11.8	470	2.5	4.5
7	R. T.	6 mo.	Infection of respiratory tract	6.8	5.30	12.5	400	2.8	5.6
8	J. A.	9 mo.	Convulsions ?	8.4	4.82	12.0	500	None	...
9	R. Th.	9 mo.	Infection of respiratory tract	10.0	4.50	9.5	600	1.0	1.6
10	J. E.	10½ mo.	Infection of respiratory tract	6.8	4.60	10.1	400	1.8	4.5
11	G. S.	11 mo.	Infection of respiratory tract	9.6	4.96	10.1	580	Trace	...
12	B. D.	13 mo.	Convalescent from pneumonia	7.9	4.72	16.0	470	Trace	...
13	R. B.	15 mo.	Impetigo	9.6	4.70	12.2	580	2.0	2.8
14	B. F.	20 mo.	Bronchiectasis	10.9	4.40	10.0	650	1.7	2.6
15	C. D.	21 mo.	Infection of respiratory tract	9.8	4.76	11.5	590	0.7	1.0
16	S. W.	2 yr.	Poliomyelitis	10.7	4.48	10.9	640	3.4	4.9
17	J. D.	2 yr.	Convulsions ?	11.6	3.80	11.0	700	2.5	3.2
18	J. W.	3 yr.	Poliomyelitis	13.5	4.22	11.5	810	1.3	1.4
19	E. M.	3 yr.	Chronic mastoiditis	14.0	3.87	11.8	840	7.2	7.2
20	C. W.	4 yr.	Tonsillitis	16.7	5.09	14.6	1,000	3.8	2.6
21	A. J.	5 yr.	Pyelitis	19.5	4.01	11.5	1,170	4.7	3.5
22	P. C.	5 yr.	Convulsions ?	16.7	3.40	10.1	1,000	2.9	2.9
23	P. Co.	6 yr.	Abdominal pain ?	16.8	5.80	12.0	1,010	4.0	3.3
24	S. T.	6½ yr.	Burns	19.0	5.00	12.0	1,140	2.1	1.5
25	N. V.	8 yr.	Eczema	23.7	5.60	10.2	1,430	4.8	3.3
26	J. S.	8 yr.	Rheumatic fever	22.6	4.85	12.0	1,380	10.0	6.1
27	J. N.	8 yr.	No disease	26.2	3.95	12.2	1,620	1.1	0.5
28	J. L.	9 yr.	Lymphangitis (arm)	28.2	3.82	12.0	1,780	3.2	1.4
29	P. K.	9 yr.	Bronchial asthma	25.4	6.50	14.8	1,580	13.0	5.6
30	A. T.	11 yr.	Pansinusitis	29.5	4.70	12.3	1,890	5.0	2.1
31	A. A.	11 yr.	Rheumatic heart disease	31.3	3.50	10.9	1,990	1.0	0.5



Comparison of the output of fecal urobilinogen of a series of normal infants and children and of several in the same age group with hemolytic disease.

said that prior to the age of 2 years most of the values were below 2.5 mg. per day, while from 3 to 11 years of age the range was usually from 2 to 7 mg. per day. (Normal adult values are from 50 to 200 mg. per day.) The hemolytic index, which was calculated when-

ever more than a trace of urobilinogen was present, was uniformly low, ranging from 0.5 to 7.2 (normal adult range, 10 to 20).

Urinary excretion of urobilinogen was studied on 6 of the children (table 5). No urobilinogen was found in the urine of 5 of the patients, and in the urine of the remaining patient, who showed 10 mg. of fecal urobilinogen per day, 1 mg. of urobilinogen was found.

Data on a group of 4 children with various hemolytic syndromes have been included (table 6) for comparison with these results. It can be seen that values for fecal urobilinogen for this group range from 44.6 to 186 mg. per day, with corresponding hemolytic indexes from 93.5 to 388. On 3 of the children splenectomy was performed with a pronounced

TABLE 5.—*Comparison of Fecal and Urinary Excretion of Urobilinogen of Control Children*

Patient *	Fecal Urobilinogen Excretion, Mg./Day	Urinary Urobilinogen Excretion, Mg./Day
20 C. W.	3.8	None
21 A. J.	4.7	None
22 P. C.	2.9	None
26 J. S.	10.0	1.0
27 J. N.	1.1	None
31 A. A.	1.0	None

* Numbers and initials refer to children as listed in table 4.

TABLE 6.—*Fecal Excretion of Urobilinogen and Hemolytic Index of Patients with Hemolytic Syndromes*

Patient	Age	Diagnosis	Weight, Kg.	Red Blood Cells, Millions	Hemoglobin, Gm.	Blood Volume, Cc.	Fecal Urobilinogen, Mg./Day	Hemolytic Index	Comment
1. C. T.	6 mo.	Acute hemolytic anemia, pneumococcic meningitis	7.8	3.58	10.2	470	44.6	93.5	Acute hemolytic anemia with hemoglobinuria, increased hypotonic fragility and spherocytosis developed during treatment with sulfadiazine and rabbit serum
2. B. J.	10 mo.	Congenital hemolytic jaundice	9.5	2.50	7.8	570	56.0 82.0	126.0 184.0	Before splenectomy
				4.00	12.5	...	13.0	18.5	After splenectomy
3. P. W.	2 yr.	Cooley's anemia	12.3	3.35	6.2	740	178.0	388.0	Before splenectomy
				3.59	5.5	...	25.0	61.2	After splenectomy performed because of symptoms due to tremendous spleen
4. M. G.	5 yr.	Sickle cell anemia	16.8	1.81 2.16	5.8 6.2	1,010 ...	103.0 186.0	176.0 297	Before splenectomy
				3.00	8.2	...	5.3	6.4	After splenectomy performed to stop repeated and severe hemolytic crises

resultant drop in the fecal excretion of urobilinogen, although the hemolytic indexes of 2 of the patients remained somewhat elevated.

COMMENT

1. *Bilirubin and Urobilinogen.*—It has long been recognized that bilirubin, rather than urobilinogen, predominates in the stools of newborn infants.[5] This is well illustrated by the results of our studies on 30 normal newborn infants, in which we found the average daily fecal bilirubin excretion for the first, second and third five day periods of life to be 8.6, 5.7 and 5.3 mg., respectively, while the fecal urobilinogen ranged from a trace to 0.70 mg. per day. It is also well established

that the appearance of urobilinogen (and the gradual disappearance of bilirubin) are linked with the development of the normal bacterial flora of the intestinal tract.[35] Urobilinogen has occasionally been reported in the meconium, but since meconium has usually been considered as sterile, other explanations, such as transfer of urobilinogen from the maternal circulation through the placenta and the production of urobilinogen in the infant's liver, have been proposed.[36] It should be stated, however, that bacteria, not of the usual colon group, have been cultured from the meconium as early as the third to the fourteenth hour of life. Thus, Passini [13] cultured the meconium of a large series of infants, with positive results in 16 per cent of the cases. Twenty-five per cent of the sterile specimens and 29 per cent of the whole group contained urobilin. The difference between these two figures is too small to show any relationship between the presence of bacteria and that of urobilin in the meconium.

We have already cited observations showing the age at which bilirubin disappears from the infant's stool. Although our work on this problem has been incomplete and adds little to what is already known, it appears that the age at which bilirubin completely disappears from the infant's stool varies within wide limits. For all practical purposes, bilirubin, except in traces, is absent from stools of infants after the seventh month of life.

Generally it can be said of the infant's stool that as the amount of bilirubin decreases the amount of urobilinogen increases. Thus, there is a reciprocal relationship between the amounts of these two pigments in the feces. This indicates that the same factors which decrease the amount of bilirubin and finally cause its disappearance are operating to increase simultaneously the amount of urobilinogen in the stool.

It is well known that the mixed bacterial flora of the intestine is largely responsible for the reduction of bilirubin to urobilinogen. This has been demonstrated repeatedly in vitro. There have been attempts to implicate single bacteria as responsible for this conversion, but the only successful results have been reported with anaerobes, such as Bacillus putrificus of Bienstock [35a] and Fränkel's gasphlegmon bacillus.[35b] Neither of these has been definitely proved responsible, and it has been suggested that they may act in symbiosis with the commonly occurring aerobic organisms.

Another factor, which probably operates through its influence on the bacterial flora, is diet. In vitro experiments have shown that the addition of carbohydrate to extracts of human stools inhibits the formation of urobilin from added bilirubin. Extracts of the stools of herbivorous animals do not possess the ability to reduce bilirubin to urobilinogen.[35a] Thus, bilirubin and biliverdin prevail in the stools of herbivora, presumably because of the predominance of fermentative processes over putrefactive. In an infant's stool, fermentation is also the main process, but this is overshadowed by putrefaction in the stools of older children and adults.

35. (*a*) Kämmerer, H., and Miller, K.: Zur enterogenen Urobilinbildung, Deutsches Arch. f. klin. Med. **141**:318-347, 1923. (*b*) Passini, F., and Czackes, J.: Ueber Urobilinbildung durch Reinkulturen anaerober Darmbakterien, Wien. klin. Wchnschr. **36**:657-659, 1923. (*c*) McMaster, P. D., and Elman, R.: Studies on Urobilin Physiology and Pathology, J. Exper. Med. **41**: 513-534, 1925; (*d*) Studies on Urobilin Physiology and Pathology: VI. The Relation of Biliary Infections to the Genesis and Excretion of Urobilin, ibid. **43**:753-783, 1926. (*e*) Bronn, G. O.; McMaster, P. D., and Raus, P.: Studies on the Total Bile: IV. The Enterohepatic Circulation of Bile Pigment, ibid. **37**:699-710, 1923. (*f*) Schmidt and Strasburger.[5d] Passini.[13]

36. Winternitz, M.: Urobilin beim Neugeborenen, Klin. Wchnschr. **5**:988-989, 1926. Lemaire.[14] Passini.[13] Passini and Czackes.[35b] Wilbur and Addis.[19] Goldschmidt-Schulhoff and Adler.[10b]

It is obvious, then, that an analogy can be drawn between infants' stools and the stools of herbivora, on the one hand, and the feces of adults and those of carnivorous animals, on the other.

The persistence of traces of bilirubin and its oxidation products in the stools of infants and the presence of urobilin later in life are adequately explained by the changing flora in the intestines. The appearance of urobilin somewhat earlier in the stools of artificially fed infants may be explained on the basis of the greater opportunity for bacterial contamination which artificial feeding affords.

2. *Urobilinogen.*—As previously stated, most of the values for fecal urobilinogen of children below the age of 2 years in our group were below 2.5 mg. per day, and for children in the 3 to 11 year group the values ranged from 2 to 7 mg. per day (normal figures for adults: 50 to 200 mg. per day). These low figures are further emphasized by the hemolytic indexes, which for most of our group ranged from 0.5 to 5.6, with only 2 children showing an index above this range, both of these being below 10, which is considered the lower limit of normal for adults. If we assume a similar type of pigment metabolism in children and in adults, the hemolytic index would be at least 10. Our values for both fecal excretion of urobilinogen and the hemolytic index, therefore, average between one fifth and one sixth of the expected value.

The cause for this distinctly lower output of urobilinogen is of some interest. Differences in the diet of older children and of adults and differences in bacterial flora are not sufficiently great to explain the great differences in fecal urobilinogen.

To rule out the possibility that the absorption of urobilinogen from the child's intestine is increased with subsequent increased excretion in the urine, the urinary excretion of urobilinogen was studied on 6 children. It was found (table 5) that the children excreted relatively less urobilinogen in the urine (as compared to the feces) than do adults. This may be due either to diminished absorption or to a difference in hepatic function.[37]

Although some evidence is present that the hemoglobin of the fetus and perhaps of the newborn infant may have a somewhat different chemical structure from adult hemoglobin,[38] no evidence exists that this difference persists into childhood. Thus, there is no basis for assuming that a difference in the chemical structure of hemoglobin plays any definite role. It is possible, however, that owing to some difference in the chemical processes within the child's intestine bilirubin is either destroyed by oxidation or changed into a form which is at present not identifiable.

The most likely possibility is that pigment metabolism in a growing child is more economical than in an adult, especially since the pigment-sparing mechanism is probably more highly developed than in adults. This would appear to be necessary when one considers that, while the adult is merely required to maintain a pigment balance, the child must provide for a rapidly expanding mass of hemoglobin and must hold on avidly to all sources for the formation of the hemoglobin molecule.

3. *Fecal Bilirubin, Urobilinogen and Hemolytic Index in the Diagnosis and Course of the Hemolytic Syndromes.*—The difference between our values for

37. Bang.[15] Opitz and Choremis.[26]

38. Dreyfus, C.: Contributions à la physiologie et pathologie des globules rouges, Schweiz. med. Wchnschr. **71**:682-689, 1941. Darling, R. C.; Smith, C. A.; Asmussen, E., and Cohen, F. N.: Some Properties of Human Fetal and Maternal Blood, J. Clin. Investigation **20**:739-747, 1941.

normal fecal excretion of urobilinogen and the figures for a small group of children with hemolytic syndromes is striking. The lowest value for fecal urobilinogen of the hemolytic group was approximately four times greater than the highest value of the control subjects, while the highest value of the hemolytic group was approximately fifteen times greater. This is even more evident when the hemolytic indexes are compared in an analogous manner. Thus, the lowest hemolytic index of the abnormal group was approximately thirteen times greater than the highest index of the control group, while the highest hemolytic index of the abnormal group was approximately fifty times greater.

For 8 of the normal newborn infants studied we had sufficient data to calculate the hemolytic index. This ranged from 0.5 to 29.7, the average being 9.6. This range and average are definitely higher than those found for the older age groups and correspond to the increased destruction of blood which occurs in the early postnatal period. For the infants with erythroblastosis studied in the accompanying paper,[39] the bilirubin excretion and the hemolytic index were also shown to be considerably increased over the normal.

It should be emphasized that if the normal adult range for fecal urobilinogen, of 50 to 200 mg. per day, is considered to be applicable to children the figures given for the group with hemolytic syndromes would be interpreted as normal. That such a transference of values is not justified is amply demonstrated by the hemolytic index. This figure relates the output of bile pigment to the total mass of circulating hemoglobin, which is in turn dependent on the total volume of blood. The hemolytic index is therefore a far more reliable measure of hemolysis than is the simple figure for fecal bilirubin or urobilinogen. This becomes particularly true in the presence of severe anemia.

The value of the estimation of fecal urobilinogen and of the hemolytic index in the follow-up of patients after splenectomy is seen in 3 of the 4 hemolytic patients presented. In the case of 1 patient (B. J.), with congenital hemolytic jaundice, the return to near normal of both the fecal urobilinogen and the hemolytic index indicates a "cure" by splenectomy. The results of splenectomy in the other 2 cases (P. W. and M. G.) indicate that destruction of blood in those hemolytic diseases which are not cured by removal of the spleen, i. e. Cooley's anemia and sickle cell anemia, can be greatly reduced by the operation. This should not be taken to mean that splenectomy is recommended as a routine procedure in cases of Cooley's anemia and sickle cell anemia.

Certain lines of investigation are immediately suggested by our results. Since the role of specific bacteria in the reduction or destruction of bilirubin is so controversial, this should be restudied. The availability of Watson's method makes the study of the fecal excretion of urobilinogen of larger series of infants and children possible. Wider application of this procedure will help to clarify many of the problems now existent.

SUMMARY AND CONCLUSIONS

The results of determinations of fecal bilirubin for a group of 30 normal newborn infants with use of the method of Malloy and Evelyn have been reported.

Study of a group of infants and children has revealed that the values for fecal excretion of urobilinogen as determined by Watson's method are much lower than would be expected when calculated on the basis of adult values.

39. Dameshek, W.; Greenwalt, T. J., and Tat, R. J.: Erythroblastosis Foetalis (Acute Hemolytic Anemia of the Newborn): Preliminary Report, Am. J. Dis. Child., this issue, p. 571.

The literature has been reviewed from the standpoints of the role of bacteria in pigment metabolism and the age at which urobilin appears and bilirubin disappears from the infant's stool.

A group of newborn infants has been studied to determine the age at which bilirubin disappears from the stool.

Values for fecal urobilinogen for a series of subjects with hemolytic disease have been reported, some with follow-up observations after splenectomy.

The value of the calculation of fecal bilirubin and urobilinogen and of the hemolytic index in the diagnosis and course of the hemolytic syndromes has been discussed.

Various lines of further investigation are suggested.

113 Bay State Road.

ERYTHROBLASTOSIS FOETALIS (ACUTE HEMOLYTIC ANEMIA OF THE NEWBORN)

PRELIMINARY REPORT

WILLIAM DAMESHEK, M.D.
BOSTON
AND
LIEUTENANT TIBOR J. GREENWALT
AND
LIEUTENANT RUSSELL J. TAT
MEDICAL CORPS, ARMY OF THE UNITED STATES

The purpose of this communication is to present evidence that erythroblastosis foetalis is primarily an acute hemolytic anemia of the newborn, due probably to an agglutinative-hemolytic process.

This concept is not new. The theory that fetal erythrocytes may enter the maternal circulation, immunize the mother and produce antibodies which subsequently pass through the placenta and act on the blood and tissues of the fetus was suggested as a cause of jaundice of the newborn by Ottenberg [1] in 1923. Hampson [2] (1929) expressed the belief that icterus gravis is the result of failure by the newborn child to produce a hypothetic antihemolytic hormone previously provided by its mother. Parsons, Hawksley and Gittins [3] and Hawksley and Lightwood [4] also went on record as regarding the intense erythroblastic reaction of the blood as secondary to a hemolytic process. Later Ross and Waugh [5] stated that there are two types of icterus gravis, obstructive and hemolytic. In a review of the various etiologic considerations of icterus gravis neonatorum, Darrow [6] concluded, although purely on logical grounds, that the underlying mechanism lies in immunization of the mother by some factor in the fetal red blood cells and that the antibodies thus formed pass through the placenta and into the colostrum and milk.

The isoimmunization theory was also used by Levine and Stetson [7] to explain the occurrence of transfusion reactions in a woman who had just given birth to

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From the Blood Laboratory of the Boston Dispensary, the Boston Floating Hospital and the Joseph H. Pratt Diagnostic Hospital.

1. Ottenberg, R.: The Etiology of Eclampsia, J. A. M. A. **81**:295-297 (July 28) 1923.
2. Hampson, A. C.: Jaundice in the Newly Born, Practitioner **131**:59-70, 1933; Grave Familial Jaundice of the Newly Born, Lancet **1**:429-432, 1929.
3. Parsons, L. B.; Hawksley, J. C., and Gittins, R.: Studies in Anemia of Infancy and Early Childhood: Hemolytic (Erythronoclastic) Anemia of Neonatal Period with Special Reference to Erythroblastosis of the New Born, Arch. Dis. Childhood **8**:159-183, 1933. Parsons, L. G., and Hawksley, J. C.: Studies in Anemias of Infancy and Early Childhood: Hemolytic (Erythronoclastic) Anemias of Later Infancy and Childhood with Special Reference to Acute Hemolytic Anemia of Lederer and Anemia of Von Jaksch, ibid. **8**:184-210, 1933.
4. Hawksley, J. C., and Lightwood, R.: A Contribution to the Study of Erythroblastosis: Icterus Gravis Neonatorum, Quart. J. Med. **3**:155-210, 1934.
5. Ross, S. G., and Waugh, T. R.: Certain Types of Icterus Gravis, Am. J. Dis. Child. **51**:1059-1082 (May) 1936.
6. Darrow, R. R.: Icterus Gravis (Erythroblastosis) Neonatorum: Etiologic Considerations, Arch. Path. **25**:378-417 (March) 1938.
7. Levine, P., and Stetson, R. E.: Unusual Case of Intragroup Agglutination, J. A. M. A. **113**:126-127 (July 8) 1939.

a macerated stillborn fetus. This patient's blood was found to contain an abnormal agglutinin which agglutinated not only her husband's red cells but 80 per cent of all other group O cells tested.

In 1940 Landsteiner and Wiener [8] demonstrated the existence of the Rh agglutinogen in the red blood cells of approximately 85 per cent of persons tested. Shortly thereafter Levine, Katzin and Burnham [9] found an atypical agglutinin in the serums of several patients who had given birth to erythroblastotic infants. These antibodies correspond in their activity to the anti-Rh agglutinin produced by Landsteiner and Wiener in animals. The hypothesis was advanced that a mother whose blood did not contain Rh agglutinogen might become immunized by a Rh-positive fetus whose blood did contain this agglutinogen, inherited from the father. When these conceptions were tested in a large series of cases, the actual findings corresponded to the theory in at least 91 per cent of the instances.[10] They were furthermore in line with the concept previously advanced by Dameshek and Schwartz [11] that in many cases hemolytic anemia is in large part due to injury of the red blood cells by isohemolysins, isoagglutinins or autoagglutinins which have for various reasons developed within the tissues.

There is much indirect evidence pointing to the hemolytic nature of erythroblastosis foetalis, i. e. the anemia, the jaundice and the indirect bilirubinemia, together with the indications of increased myeloid regenerative activity in the peripheral blood, such as the presence of nucleated red cells, reticulocytes and myelocytes. The extreme erythroblastic hyperplasia of the bone marrow and the marked extramedullary hemopoiesis in the spleen and liver are also indicative of the reaction to a hemolytic process. However, direct proof of the hemolytic nature of the disease must lie in the quantitative demonstration of increased excretion of derivatives of the breakdown of hemoglobin, i. e. bilirubin and its products. The present communication deals with such determinations in 3 successive cases of erythroblastosis foetalis.

PRODUCTS OF THE BREAKDOWN OF HEMOGLOBIN

The large mass of substances formed by the breakdown of hemoglobin is excreted in the feces. The amounts excreted in the urine are relatively insignificant, and our studies have therefore been limited to the fecal values.

In an adult, the bilirubin excreted in the bile is reduced to urobilinogen by the action of intestinal bacteria. Urobilinogen is rapidly oxidized to urobilin when exposed to air. Except perhaps in traces, neither bilirubin nor biliverdin is found in the stool of an adult. In a newborn infant, on the contrary, the bulk of pigment

8. Landsteiner, K., and Wiener, A. S.: Agglutinable Factor in Human Blood Recognized by Immune Sera for Rhesus Blood, Proc. Soc. Exper. Biol. & Med. **43**:223, 1940; Studies on an Agglutinogen (Rh) in Human Blood Reacting with Anti-Rhesus Sera and with Human Iso-Antibodies, J. Exper. Med. **74**:309-320, 1941.

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10. Levine, P.; Vogel, P.; Katzin, E. M., and Burnham, L.: Pathogenesis of Erythroblastosis Foetalis: Statistical Evidence, Science **94**:371-372, 1941. Levine, P.; Burnham, L.; Katzin, E. M., and Vogel, P.: The Role of Iso-Immunization in the Pathogenesis of Erythroblastosis Foetalis, Am. J. Obst. & Gynec. **42**:925-937, 1941. Hooker, S. B.: Iso-Immunization in Relation to Intragroup Hemolytic Transfusion Reactions, New England J. Med. **225**:871-877, 1941.

11. Dameshek, W., and Schwartz, S. O.: The Presence of Hemolysins in Acute Hemolytic Anemia: Preliminary Note, New England J. Med. **218**:75-80, 1938; Hemolysins as the Cause of Clinical and Experimental Anemia, Am. J. M. Sc. **196**:769-792, 1938; Acute Hemolytic Anemia, Medicine **19**:231-327, 1940.

is present in the form of bilirubin and biliverdin, urobilinogen being either absent or demonstrable only in traces. With the development of the intestinal flora after the early days of life, bilirubin and its oxidation products gradually disappear and are replaced by urobilinogen, albeit in small amount.[12] Since some observers believe that fetal hemoglobin may differ in structure from that found after birth, it is possible that differences in the makeup of the fecal pigment in the stools of newborn infants and of adults may be of a more fundamental character.[13]

Relatively few reports [14] of the excretion of bilirubin and urobilin by the newborn have been made. These have been reviewed in a previous paper, together with the results of our study of the excretion of bile pigments in the stools of 30 normal newborn infants.[12e] In this paper, we have compared the fecal output of urobilinogen and bilirubin of 3 infants with erythroblastosis foetalis with that of our series of normal newborn infants.

METHODS

Determinations of fecal bilirubin were performed by the method of Malloy and Evelyn.[15]

Fecal urobilinogen was estimated by the method of Watson,[16] which is a modification of Terwen's method.[17]

The hemolytic index, as suggested by Belonogowa [18] and by Singer, Miller and Dameshek,[19] was calculated from the formula

$$\frac{\text{Total bilirubin + total urobilinogen per day in milligrams} \times 100}{\text{Total circulating hemoglobin in grams}}$$

The hemolytic index expresses the number of milligrams of bile pigment derived from each 100 Gm. of circulating hemoglobin and is therefore a far better indicator of the degree of

12. (*a*) Zweifel, P.: Untersuchungen über das Meconium, Arch. f. Gynäk. **7**:474-490, 1875. (*b*) Schmidt, A., and Strasburger, J.: Die Fäzes des Menschen, ed. 4, Berlin, August Hirschwald, 1915, pp. 268-281. (*c*) Schorlemmer, R.: Ueber den Nachweis von Gallenfarbstoff in den Faeces, insonderheit mit der Ad. Schmidt'schen Probe, und über die klinische Bedeutung des Vorkommens von Bilirubin in denselben, Arch. f. Verdauungskr. **6**:263-284, 1900. (*d*) Simon, cited by Ylppö.[14a] (*e*) Tat, R. J.; Greenwalt, T. J., and Dameshek, W.: The Output of Bile Pigment by Newborn Infants and by Older Infants and Children, this issue, p. 558.

13. Darling, R. C.; Smith, C. A.; Asmussen, E., and Cohen, F. M.: Some Properties of Human Fetal and Maternal Blood, J. Clin. Investigation **20**:739-747, 1941. Dreyfus, C.: Contributions à la physiologie et pathologie des globules rouges, Schweiz. med. Wchnschr. **71**:682-689, 1941.

14. (*a*) Ylppö, A.: Icterus Neonatorum (incl. I. n. gravis) und Gallenfarbstoffsekretion beim Foetus und Neugeborenen, Ztschr. f. Kinderh. **9**:208-318, 1913. (*b*) Snelling, C. E.: Icterus Neonatorum, J. Pediat. **2**:399-413, 1933. (*c*) Ross, S. B.; Waugh, T. R., and Malloy, H. T.: The Metabolism and Excretion of Bile Pigments in Icterus Neonatorum, ibid. **11**: 397-408, 1937. (*d*) Giaume, C., and Lanza, P.: Determinazione quantitativa della bilirubina nel meconio e nelle feci del lattante, Pediatria **37**:519-534, 1929. (*e*) Dordi, A. M., and Rossi, G.: Sul ricambio emoglobinico nel lattante e nel bambino normale, Riv. di clin. pediat. **34**:594-600, 1936. (*f*) Kerppola, W., and Leikola, E.: Zur Chemie des Bilirubins; die Bestimmung des Bilirubins in den Körperflüssigkeiten, mit seiner Eigenfarbe und der Diazofarbe als Massstab; ein neues, quantitatives Extraktionsverfahren, Acta med. Scandinav. **78**:24-41, 1932.

15. Malloy, H. T., and Evelyn, K.: Oxidation Method for Bilirubin Determinations in Bile and Meconium with the Photoelectric Colorimeter, J. Biol. Chem. **122**:597-603, 1938.

16. Watson, C. J.: Studies of Urobilinogen: I. Improved Method for Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**:458-475, 1936.

17. Terwen, A. J. L.: Ueber ein neues Verfahren zur quantitativen Urobilinbestimmung in Harn und Stuhl, Deutsches Arch. f. klin. Med. **149**:72-101, 1925.

18. Belonogowa, N. S.: Ueber den Blutumsatz bei verschiedenen Anämien und die Beeinflussung desselben durch die Behandlung mit Bluttransfusion, Salvarsan, Arsen, Eisen, und Leberdiät, Deutsches Arch. f. klin. Med. **162**:297-329, 1928.

19. Singer, L.; Miller, E. W., and Dameshek, W.: Hematologic Changes Following Splenectomy in Man, with Particular Reference to the Target Cell, Hemolytic Index, and Lysolecithin, Am. J. M. Sc. **202**:171-187, 1941.

hemolysis than is the figure for the total daily excretion of the hemoglobin derivatives alone. Values for bilirubin and urobilinogen have been used interchangeably, because these substances differ so little in molecular weight that it is not necessary to distinguish between them in applying this formula.

In determining the total circulating hemoglobin, which requires knowledge of the total blood volume, the data of Brines, Gibson and Kunkel,[20] who studied the blood volume in newborn infants and children, were used.

RESULTS

The results of the determinations of fecal bilirubin of our series of normal newborn infants have been reported in another article.[12e] They are repeated here in tabular form for convenience in comparing them with the values obtained for the erythroblastotic infants (table 1).

TABLE 1.—*Comparison of Certain Factors Relating to Hemolysis in Normal and in Erythroblastotic Infants*

Patient	Day of Life	Red Blood Cells, Millions	Hemoglobin, Gm.	Serum Bilirubin, Mg./100 Cc.	Total Stool Pigment, Mg./Day	Hemolytic Index *
			Normal Infants (None Jaundiced)			
1	10	6.38	19.4	...	8.8	15.1
2	7	6.90	22.9	...	8.6	12.5
3	5	6.35	21.9	...	19.5	29.7
4	10	6.37	20.8	...	1.6	2.6
5	9	6.87	20.4	...	2.3	3.7
6	8	5.43	16.5	...	0.3	0.5
7	11	6.06	20.8	1.8	3.8	6.1
8	11	5.92	18.1	0.2	3.8	7.0
			Erythroblastotic Infants			
Vr.	6-10	1.48	4.6	3.9 (indirect)	40.5	293.0
	17-21	1.44	5.4	.....	40.4	249.0
	22-25	1.79	5.8	.....	49.9	287.0
	26-29					
W.	19-21	2.04	7.1	6.4 (direct) (indirect)	30.3	142.0
	26-30	1.81	7.1	10.6 (direct) (indirect)	27.0	127.0
	31-34	2.81	7.3	5.8 (direct) (indirect)	40.3	184.0
R.	3	4.46	13.2	.....	36.0	91.0
	4	....	....	.....	109.0	287.0
	9	3.16	9.1	.....	19.4	71.0
	11-12	3.49	9.4	.....	79.9	283.0

* Volume of blood was considered to be 300 cc. in this calculation.

For the normal group, from the first to the fifth day of life the bilirubin values ranged from 1.0 to 23 mg. per day, with an average excretion of 8.6 mg.; in the next five day period the range was 0 to 16 mg. per day, with an average excretion of 5.7 mg., and from the tenth to the fifteenth day the range was 0.3 to 12.4 mg. per day, with an average excretion of 5.3 mg. The hemolytic indexes of these infants ranged from 0.5 to 29.7, with an average of 9.6.

In the 3 cases of erythroblastosis foetalis reported later in this study, the fecal bilirubin excretion ranged from 19.4 to 109.0 mg. per day during an analogous period, i. e. in the first fifteen days of life. The hemolytic index was extremely high, ranging from 71.0 to 293.0 in the same period.

Values for the fecal excretion of urobilinogen by the normal infants ranged from a trace of 0.70 mg. per day, while the erythroblastotic infants excreted from 0.25 to 11.0 mg. per day.

20. Brines, J. K.; Gibson, J. G., and Kunkel, P.: The Blood Volume in Normal Infants and Children, J. Pediat. **18**:447-457, 1941.

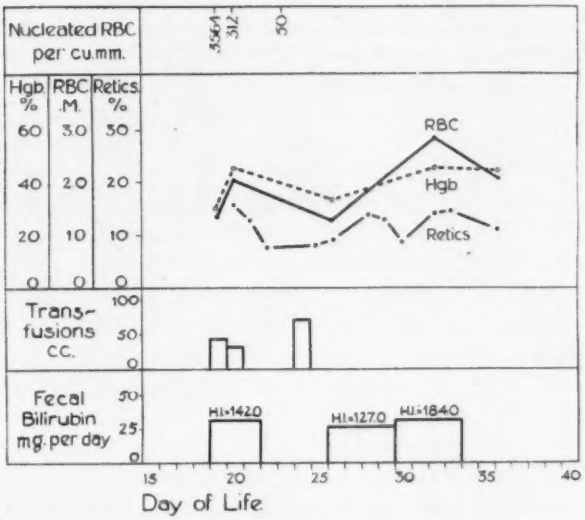

Chart 1.—Condition of the blood and fecal output of bilirubin of Baby W., with erythroblastosis foetalis. The hemolytic index (H. I.) varied between 127 and 184 mg. per hundred grams of circulating hemoglobin, the average normal in our series being 9.6 mg.

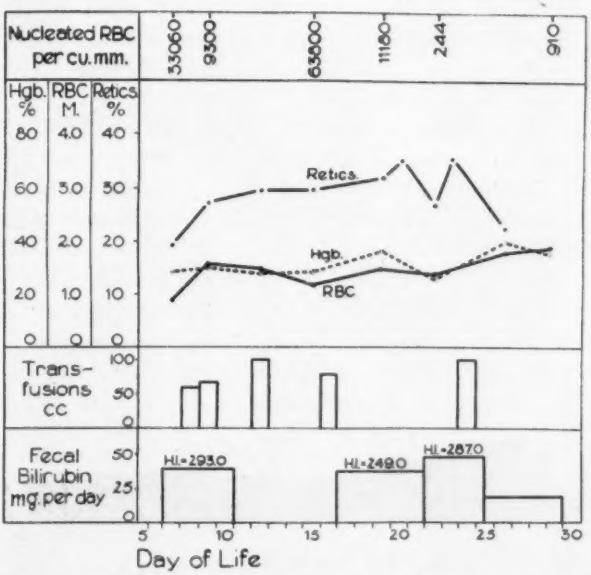

Chart 2.—Condition of the blood and fecal output of bilirubin of Baby V., with erythroblastosis foetalis. The hemolytic index (H. I.) varied between 249 and 293 mg. per hundred grams of circulating hemoglobin, the average normal in our series being 9.6 mg.

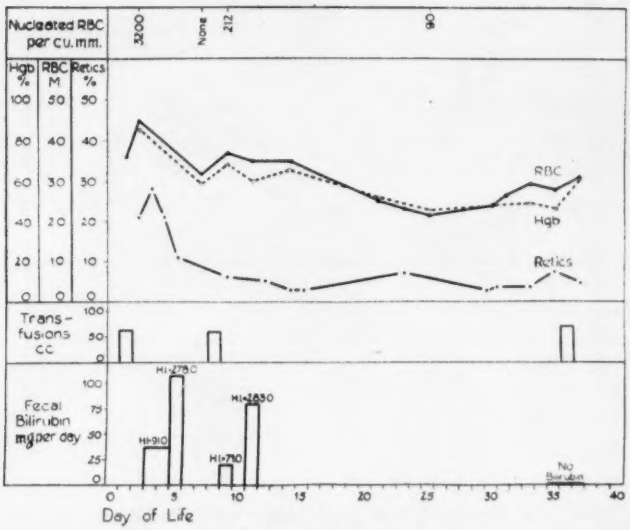

Chart 3.—Condition of the blood and fecal output of bilirubin of Baby R., with erythroblastosis foetalis. The hemolytic index (H. I.) varied between 71 and 283 mg. per hundred grams of circulating hemoglobin, the average normal in our series being 9.6 mg.

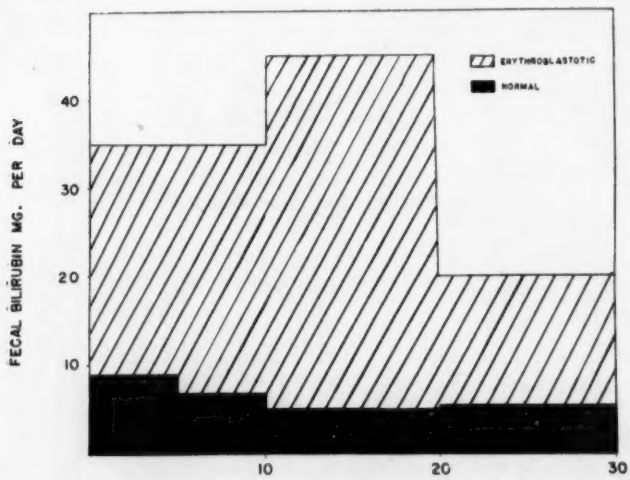

Chart 4.—A comparison of the fecal output of bilirubin of normal and of erythroblastotic infants. The bilirubin output of the erythroblastotic infants was extremely high as compared with that in the normal infants.

COMMENT

In the 3 cases of erythroblastosis foetalis reported here, all the typical features of the condition were present: jaundice occurring at or shortly after birth, hepatomegaly and splenomegaly, anemia, leukocytosis, erythroblastosis and a leukemoid type of white cell reaction. Opportunity for study of the Rh factors was present in cases 2 and 3. The results in case 2 were unusual in that the blood of the mother and the child contained Rh agglutinogen while that of the father did not; in case 3, however, there was the usual situation, i. e. that the mother did not have agglutinogen in her blood but the father and the fetus did. As already stated, we have interpreted the anemia and jaundice as the results of a hemolytic process, the reticulocytosis, leukocytosis and leukemoid blood picture indicating pronounced regenerative activity of the bone marrow in response to the increased breakdown of blood. That this is probable is further confirmed by postmortem observations, which show an intense erythroblastic reaction of the bone marrow, with extensive myeloid metaplasia in the liver and spleen and not infrequently in other organs.

The concept that erythroblastosis foetalis is primarily a hemolytic process has been advanced by various workers.[21] However, this view has been opposed by Diamond, Blackfan and Baty [22] and Diamond.[23] Because of the presence of bile in the urine and direct—as well as indirect—bilirubinemia, the possibility of an obstructive or hepatic jaundice due to severe hepatitis has been suggested.[24] Discovery of the importance of the Rh factor and development of the concept of isoimmunization by Levine and his co-workers have brought the hemolytic concept sharply to the foreground. Dameshek and Schwartz [11] suggested that in many cases hemolytic anemia is due to the activity of autohemolysins within the body and cited several cases in which an isohemolysin was present in the patient's blood serum. These workers produced hemolytic anemias of varying degrees of severity in guinea pigs by injecting immune heterohemolytic serum. In other experiments, Dameshek and Miller [25] demonstrated that hemolysins, both simple and complex, and agglutinins act on red blood cells, injuring them so that they become susceptible to the activities of complement, erythrostasis, mechanical trauma within the circulation, etc. It was believed that similar mechanisms might hold true in erythroblastosis foetalis, as Levine and his co-workers had already suggested. The development of an anti-Rh agglutinin in the mother through isoimmunization might result in injury to the Rh-positive red cells of the fetus within the placenta and in their subsequent hemolysis through the factors of mechanical trauma and erythrostasis in the fetal and placental circulation.

Although the exact nature of the hemolytic mechanism in erythroblastosis foetalis may be disputed, the results of our present studies indicate strongly that the condition is fundamentally one of increased breakdown of blood. The excretion of bilirubin and its derivatives in the stools of the erythroblastotic infants far

21. Hampson.[2] Ross and Waugh.[5] Darrow.[6]

22. Diamond, L. K.; Blackfan, K. D., and Baty, J. M.: Erythroblastosis Fetalis and Its Association with Universal Edema of the Fetus, Icterus Gravis Neonatorum, and Anemia of the New Born, J. Pediat. **1**:269-309, 1932.

23. Diamond, L. K.: Round Table Discussion of Disorders of Blood, J. Pediat. **7**:418-426, 1935. The Erythroblastic Anemias, or, Anemias Associated with Erythroblastosis, in A Symposium on the Blood and Blood-Forming Organs, Madison, University of Wisconsin Press, 1939, pp. 66-67.

24. Klemperer, P.: Icterus Gravis of the New-Born, Am. J. Dis. Child. **28**:212-226 (Aug.) 1924. Ross and Waugh.[5]

25. Dameshek, W., and Miller, E. B.: The Pathogenesis of the Hemolytic Syndromes, Arch. Int. Med., to be published.

exceeded that of a control series of normal newborn infants. Thus, the lowest hemolytic index for any of the 3 erythroblastotic infants was approximately 2.5 times greater than the highest value for the series of normal infants. The highest hemolytic index for the erythroblastotic group was approximately 10 times greater than the corresponding figure for the normal series. Miller, Singer and Dameshek [19] have shown that the most important indication of the degree of breakdown of blood is the hemolytic index, which is derived from the figures for fecal urobilinogen and blood volume. The findings in our cases of erythroblastosis foetalis thus indicate a fulminating hemolytic process comparable in severity to that seen in the hemolytic crises of hereditary spherocytic hemolytic jaundice and in acute acquired hemolytic anemia.

The type of anemia in the disease is also similar to that found in acute hemolytic anemia, i. e. normomacrocytic, or what Dameshek and Schwartz have called "pseudomacrocytic" (i. e. there is apparent macrocytosis which is due chiefly to the presence of large numbers of reticulocytes). A biphasic Price-Jones curve

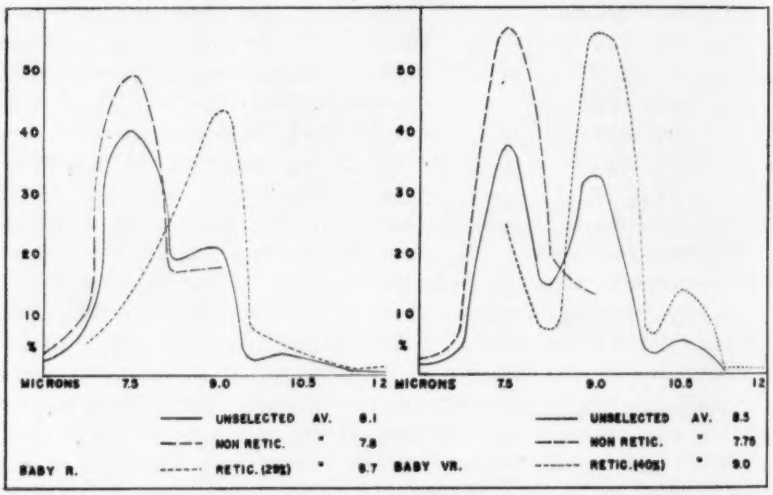

Chart 5.—Price-Jones curves for erythroblastosis foetalis. The "pseudomacrocytic" blood picture and the biphasic curve as seen in hemolytic anemia are illustrated. The reticulocytes are definitely larger than mature red cells and result in apparent macrocytosis.

of red cell diameters is produced (chart 5), which has been emphasized by these authors and by Tigertt and Duncan [26] and others as characteristic of experimental and clinical hemolytic syndromes.[27]

The matters of the type of bilirubinemia—direct or indirect—and of the bilirubinuria are of some interest. The presence of bile in the urine and of a direct van den Bergh reaction of the blood is ordinarily sufficient to exclude a hemolytic process. However, we have encountered a similar situation in other typical hemolytic processes with which an associated hepatic disturbance was

26. Tigertt, W. D., and Duncan, C. N.: Erythrocyte Morphology in Experimental Hemolytic Anemia as Induced by Specific Hemolysins, Am. J. M. Sc. **200**:173-182, 1940.

27. In an article which appeared while the present paper was in press, Reisner emphasized the biphasic character of the Price-Jones curves in erythroblastosis foetalis as evidence of the hemolytic character of the disease (Reisner, E. H., Jr.: Morphology of Erythrocytes in Erythroblastosis Foetalis, Arch. Int. Med. **71**:230-255 [Feb.] 1943).

present. Thus, in 2 recent cases studied, direct as well as indirect bilirubinemia was present; in 1 there was pronounced myeloid metaplasia of the liver, and in the other a severe acute hepatitis was discovered at postmortem examination. The extensive myeloid metaplasia of the liver in erythroblastosis foetalis has already been mentioned, and it is possible that the direct bilirubinemia is due partly to alteration of the architecture of the liver by the myeloid metaplasia with resultant "regurgitation" of the direct bilirubin into the blood [22] and partly to inability of the newborn infant's liver to cope with the large amounts of bilirubin suddenly brought to it. Direct bilirubinemia is always productive of bile-stained urine.

That erythroblastosis foetalis is simply acute acquired hemolytic anemia of the newborn is thus borne out by various pieces of evidence, direct and indirect. The leukoerythroblastic blood picture and the marked myeloid metaplasia of the liver and spleen are probably the results of the extraordinary regenerative capacity of the newborn infant's blood-forming tissues. The evidence indicating the hemolytic nature of erythroblastosis foetalis is presented in table 2.

TABLE 2.—*Evidences of the Hemolytic Nature of Erythroblastosis Foetalis*

Symptoms and Signs	Direct Evidences of Increased Destruction of Blood	Indirect Evidences of Increased Destruction of Blood	Etiologic Mechanism
Acute onset	Anemia	Pseudomacrocytic blood picture; biphasic Price-Jones curves	Isoimmunization of mother whose blood did not contain Rh agglutinogen by fetus with Rh agglutinogen in blood; development of anti-Rh agglutinin
Jaundice	Icterus	Reticulocytosis	
Pallor	Indirect bilirubinemia	Erythroblastosis	
Splenomegaly	Fecal bilirubin +++	Leukocytosis	
Hepatomegaly	Hemolytic index 2.5 to 10 × high normal values	Leukemoid blood picture	Agglutination of fetus' red cells by agglutinin; subsequent hemolysis
		Myeloid metaplasia of the spleen and liver	

REPORT OF CASES

CASE 1 (chart 1).—Baby R. was referred to the Boston Floating Hospital on July 17, 1941, four hours after birth, because of jaundice. The mother had been delivered two weeks before term by cesarean section because of the unfortunate results of two previous pregnancies, the first child having died a day after birth with a congenital cardiac defect and the second having been stillborn at full term.

On admission the baby weighed 5 pounds 12 ounces (2,508 Gm.). There was severe icterus; the cry was weak, and the eyelids were somewhat edematous. The liver was felt 2 fingerbreadths below the right costal margin, while the spleen was just palpable under the left costal margin.

Although the initial hemoglobin content and red cell count were 85 per cent (13.2 Gm.) and 4,460,000 respectively, these levels were not maintained, despite two blood transfusions of 60 cc. each. The jaundice had cleared by the sixth day in the hospital, but the pallor increased gradually; on the twenty-fifth day in the hospital the red cell count was 2,130,000 and the hemoglobin content was 44 per cent (6.8 Gm.). The white cell count was 32,000 (corrected for nucleated red cells) on admission but had returned to normal levels after the first week of hospitalization. The platelets ranged from 300,000 to 830,000 (normal 500,000 to 900,000). The reticulocytes were 21 per cent on admission and remained moderately elevated during the child's entire stay in the hospital. The differential counts consistently revealed the presence of 1 to 6 per cent of metamyelocytes, 1 to 7 per cent of myelocytes and an occasional myeloblast. On admission 3,200 nucleated red cells per cubic millimeter were present, and on the twenty-fifth day 90 per cubic millimeter were still present. The urine gave a negative reaction for bilirubin (Gmelin's test). The fecal excretion of bilirubin varied between 18.4 and 106.8 mg. per day and the urobilinogen excretion between 0.28 and

2.9 mg. per day. The hemolytic index varied between 71.0 and 283.0 (normal average 10). The blood of both the patient and her mother belonged to group A (Moss II); the Rh factors were not determined. Serologic reactions were normal.

The patient was placed in an oxygen tent and given vitamin K intramuscularly on admission. There was continued improvement, but the anemia which developed failed to respond to iron and to parenterally administered liver extract. On the thirty-sixth day in the hospital an infection of the upper respiratory tract developed and a third transfusion, of 70 cc., was given. The blood of donors was cross matched by the Landsteiner test tube technic, incubation of the serum–red cell–sodium chloride mixture being maintained at 37 C. for at least thirty minutes.

The patient was discharged on the forty-third hospital day much improved. The weight at the time of discharge was 7 pounds 10 ounces (3,460 Gm.).

CASE 2 (chart 2).—Baby Vr. was admitted to the Boston Floating Hospital on Oct. 1, 1941, at the age of 6 days. At birth the amniotic fluid and vernix caseosa were noted to be highly colored but the placenta was reported as grossly normal. Jaundice had been noted at birth and had become progressively more severe, with a change of the infant's color from yellowish to waxy and with increasing lassitude. The mother had had a miscarriage with her first pregnancy of this marriage but had had two normal pregnancies by another marriage.

On admission, pallor and a yellowish waxy color were noted. The liver was felt 2 fingerbreadths below the right costal margin, and the spleen was noted to be enlarged.

On admission, the red cell count was 890,000 per cubic millimeter, the hemoglobin 28.2 per cent (4.4 Gm.), the white cell count 58,000 (corrected for nucleated red cells), the platelets 385,000, the reticulocytes 19.7 per cent and the nucleated red cells 33,060 per cubic millimeter. The hypotonic fragility began with a 0.5 per cent solution of sodium chloride and was complete with a 0.22 per cent concentration. The serum bilirubin on one occasion was 3.9 mg. per hundred cubic centimeters (indirect). The differential counts on various occasions revealed 2 to 6 metamyelocytes, 2 to 6 myelocytes and 3 to 6 myeloblasts. The baby's blood belonged to group A (Moss II) and contained Rh agglutinogen. The blood of the mother also was of group A and contained Rh agglutinogen, while that of the father was of group O (Moss IV) and did not contain Rh agglutinogen. No cold or warm isoagglutinins and autoagglutinins or hemolysins were demonstrable in the serum of the patient. The serologic reactions of the patient were normal. A culture of blood yielded no organisms. The urine on one occasion gave a positive reaction for bilirubin by a foam test.

Pneumonia involving the lower lobe of the right lung developed on the patient's second day in the hospital and was treated with sulfadiazine, the child being placed in an oxygen tent. Five transfusions of compatible blood without Rh agglutinogen were given, with no remarkable improvement in the patient's blood picture. The red cell count fluctuated between 1,100,000 and 1,200,000 and had risen only slightly, to 1,900,000, just before discharge. The nucleated red cells at one time reached a peak of 63,000 per cubic millimeter, and there were still 910 per cubic millimeter at the time of discharge. The reticulocyte count ranged between 27 and 35.8 per cent and was at its lowest level, 16.3 per cent, just before discharge. The fecal excretion of bilirubin ranged from 17.3 to 48.0 mg. per day. The corresponding hemolytic indexes ranged from 249.0 to 293.0 (normal 10 to 20).

The patient gradually improved clinically, and during her hospitalization her weight increased from 7 pounds 14 ounces to 9 pounds (3,572 to 4,082 Gm.). She was discharged on the twenty-fifth day of hospitalization.

CASE 3 (chart 3).—Baby W. was referred to the Boston Floating Hospital on Sept. 22, 1941, at the age of 18 days. Jaundice had been noted on the second day of life. The mother had had one previous normal pregnancy.

On admission the patient appeared well nourished and not in acute distress. Intense icterus was, however, present. The liver was felt just below the right costal margin and the spleen 1 to 2 fingerbreadths below the left costal margin. The weight on admission was 8 pounds 10 ounces (3,912 Gm.).

On admission the red cell count was 1,350,000; the hemoglobin content, 30 per cent (4.7 Gm.); white cell count, 16,200 (corrected for nucleated red cells); the reticulocyte count, 16.0 per cent, and platelet count, 261,000. The hypotonic fragility began with a 0.44 per cent and was complete with a 0.2 per cent solution of sodium chloride. Differential white cell counts were not abnormal, and the total leukocyte count remained at normal levels. On admission 3,564 nucleated red cells per cubic millimeter were present, but these rapidly disappeared. The serologic reactions and the results of urinalysis were normal. The baby, its mother and its father all had blood belonging to group A (Moss II). The blood of the

mother did not contain Rh agglutininogen, while both that of the baby and that of the father did. An anti-Rh agglutinin was demonstrated in the mother's serum. The bilirubin level of the serum fluctuated between 5.8 and 10.6 mg. per hundred cubic centimeters and gave both direct and indirect van den Bergh reactions. The fecal excretion of bilirubin varied between 24 and 30 mg. per day, while the urobilinogen output varied between 0.25 and 11 mg. per day. The corresponding hemolytic indexes ranged from 127.0 to 184.0 (normal 10 to 20).

The patient was given three transfusions of compatible blood that did not contain Rh agglutinogen. The highest erythrocyte count was 2,800,000, but at the time of discharge the count was only 2,100,000. The percentage of reticulocytes remained elevated and was 11.3 on discharge. The platelet count reached a peak of 1,175,000 on one occasion.

The patient was discharged on the twentieth day of hospitalization, weighing 10 pounds (4,536 Gm.).

SUMMARY

On the basis of quantitative studies of the excretion of bilirubin and urobilinogen by newborn infants, 3 of them with erythroblastosis foetalis, the conclusion is drawn that this condition is a severe and acute hemolytic anemia of the newborn.

The direct and indirect evidences of increased hemolysis are cited, and the pathogenetic mechanisms relating erythroblastosis foetalis to other types of acute acquired hemolytic anemia are discussed.

Case Reports

PAROXYSMAL TACHYCARDIA IN A TWO MONTH OLD INFANT WITH A VENTRICULAR RATE OF 350

JOHN P. HUBBARD, M.D.
AND
GEORGE W. STARBUCK, M.D.
BOSTON

The following case is presented, first, to call attention to the syndrome and treatment of paroxysmal tachycardia in young infants and, secondly, because of the remarkably rapid ventricular rate, of 350, which, as far as we are aware, is faster than any previously recorded.

Paroxysmal tachycardia as it appears in young infants has been reviewed in an earlier communication.[1] It was shown to have a distinctive clinical syndrome and to respond satisfactorily to digitalis therapy. Also the fact that a series of 9 cases could be collected over a relatively short time suggested that the condition may occur more often than has been recognized. This is borne out by a number of additional cases which have come to our attention since the earlier report. One of these has been published by Hobbs [2] and serves to illustrate, as does also the following case, the characteristic features.

REPORT OF A CASE

E. E., a boy, was born on Feb. 5, 1941, after a long, difficult instrumental delivery. The baby appeared well at birth and was considered normal by his attending physician. He progressed satisfactorily during his first four weeks of life. On March 3, at the age of 4 weeks, he started vomiting almost all of his feedings and rapid respirations developed. This continued for the following four days, until March 7, when he was admitted to a local hospital. At that time he appeared cyanotic and had rapid grunting respirations. The lungs were reported as clear. His heart rate was recorded as 200. No murmurs were heard. The abdomen was distended. He was considered in a critical condition. Dextrose solution was given by hypodermoclysis. He gradually improved without any further specific therapy and was discharged on March 12 with a diagnosis of "feeding problem."

The baby then progressed satisfactorily at home until April 17, when he again started to vomit and became comatose. He was promptly (a few hours later) readmitted to the same hospital. There was again cyanosis, accompanied with a "cold sweat." He did not, however, at this time appear acutely ill. The pulse rate was 200 and the respirations rapid. There was a discharge from the left eye. The fontanel was considered as slightly bulging. The liver was thought to be enlarged, and there was fluid in the scrotum, which was attributed to a hydrocele. The diagnoses which were considered at this time were meningitis and a blood dyscrasia. The temperature had risen to 102.5 F. On April 20 the patient was transferred to the Infants' Hospital.

On his admission to the Infants' Hospital the temperature was 101 F., the respiratory rate 60 and the pulse so rapid that an accurate count was impossible. On physical examination there were no meningeal signs; the anterior fontanel did not appear tense or bulging. The lungs were resonant and free from rales. The heart was enlarged to palpation and percussion. The rhythm was regular and extremely rapid, giving a tic-tac sound. No murmurs could be distinguished. The abdomen was distended, with the edge of the liver felt at the level of the umbilicus. The urine was normal except for a faint trace of albumin. The hemoglobin

From the Department of Pediatrics, Harvard Medical School, and the Infants' Hospital and Children's Hospital.

1. Hubbard, J. P.: Paroxysmal Tachycardia and Its Treatment in Young Infants, Am. J. Dis. Child. **61**:687-709 (April) 1941.

2. Hobbs, L. F.: Paroxysmal Tachycardia in Infancy, Am. Heart J. **21**:804-806 (June) 1941.

content was 60 per cent; the erythrocyte count was 3,600,000 per cubic millimeter, and the white cell count was 15,500 per cubic millimeter, with 62 per cent neutrophilic leukocytes. An electrocardiogram taken directly after admission showed paroxysmal tachycardia of supraventricular origin with a ventricular rate of 350 (fig. 1).

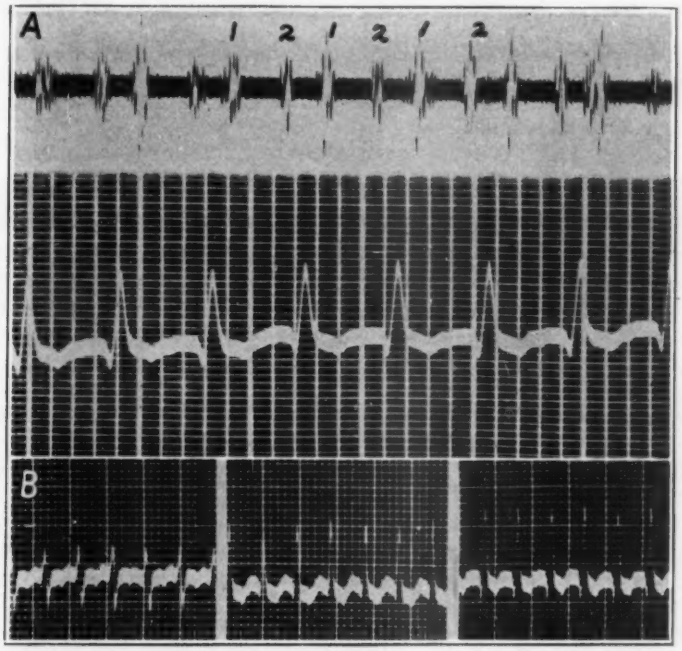

Fig. 1.—*A*, phonocardiographic tracing taken from the precordial area with lead II, showing a ventricular rate of 353. The camera is speeded up to three times the usual rate, which is shown below. The sound tracing shows first and second sounds in rapid succession, with systole of longer duration than diastole. *B*, the three standard leads show paroxysmal tachycardia of supraventricular origin with right axis deviation.

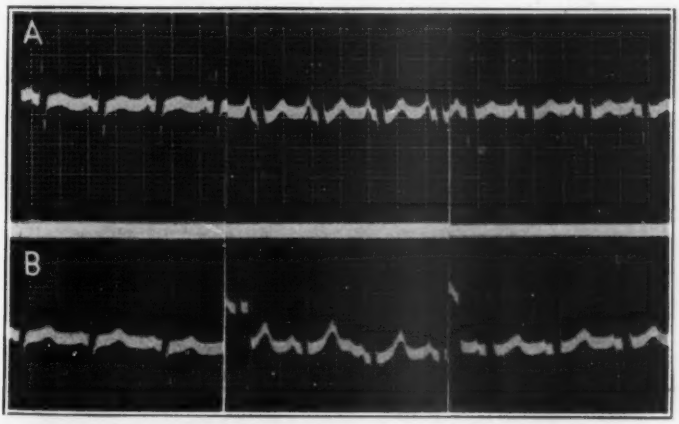

Fig. 2.—*A*, tracing taken twenty-two hours after figure 1, showing satisfactory response to digitalis. *B*, normal record two months later.

Following the diagnosis of paroxysmal tachycardia, digitalis therapy was started with an initial dose of 1 cc. of digifolin solution (0.1 Gm. of digifolin, equivalent to ½ cat unit) given intravenously. A further dose of 1 cc. was given intramuscularly four hours later in view of the persistence of the tachycardia. After this second dose the tachycardia stopped and the

pulse rate dropped to 160 (fig. 2 *A*). Twelve hours after the first dose, there was a recurrence of the tachycardia, for which a further dose of 1 cc. of digifolin in solution was given intramuscularly. The pulse rate promptly dropped to a normal level again and thereafter remained normal. With the improvement in the pulse rate, there was an increasing improvement in the respiratory rate. The temperature, which in the first twelve hours fluctuated from 101 to 102 F., fell to normal. The liver decreased in size, and the baby made an uneventful recovery.

At the present writing, seven months has elapsed since this episode without any recurrence of the tachycardia. The baby is progressing satisfactorily and is apparently normal in all respects. There are no heart murmurs or any other evidence of cardiac difficulty. Recent electrocardiograms have been normal.

SUMMARY

In a case of paroxysmal tachycardia in a 2 month old infant a remarkably rapid ventricular rate of 350 was demonstrated electrocardiographically.

This case illustrates the distinctive syndrome of congestive heart failure resulting from paroxysmal tachycardia in young infants, which is characterized by rapid respirations, prostration, ashen cyanosis, vomiting, fever, engorgement of the liver, dilatation of the heart, pulmonary congestion and an excessively rapid heart rate.

The satisfactory response to digitalis is also shown.

319 Longwood Avenue.

POSTINFECTIOUS ENCEPHALOMYELITIS

REPORT OF ITS OCCURRENCE FOLLOWING MEASLES AND VACCINATION FOR SMALLPOX, WITH COMPLICATING BROMIDE POISONING

PAULINE GEORGE STITT, M.D.
BUFFALO

Recent years have seen increased interest in postinfectious and postvaccinal encephalitis and realization of the prevalence of bromide poisoning. A case is presented in which these conditions occurred simultaneously.

REPORT OF A CASE

W. W., a 9 year old white boy, was first seen Aug. 2, 1939. The chief complaint was "jerking and twitching" of six weeks' duration.

History.—Fifteen weeks earlier he had contracted measles and was moderately ill. He stayed in bed one week but was out of school two weeks longer because of excruciating headaches, which started about a week after the onset of measles. The headaches were severe enough to make him stop whatever he was doing and run to lie down. They occurred every day or two and lasted from three hours to a day. There was occasional nonprojectile emesis. He received pills (nature unknown) for the pain but obtained no relief. After two weeks, the headaches subsided and he returned to school, apparently fully recovered although somewhat listless.

One week after returning to school he was vaccinated for smallpox. He had a good "take" but was not ill with it. Two weeks later, about the time the vaccination crust came off, he began to drop everything he touched, became unable to feed himself and fell when he tried to walk. There were no convulsions or loss of consciousness, but according to his mother he was unable to sleep night or day for three days. He was given some sedative in tablet form (nature unknown) three or four times a day. After several days a rash appeared. It was described as "a thick rash that stood up all over the body and when it disappeared left brownish black stains." His condition became progressively worse. The sedative was used freely, and when it seemed ineffectual the mother increased the prescribed dose and used it more frequently. The boy remained wakeful. The uncontrollable movements became worse, and he was no longer able to speak or swallow.

Physical Examination.—He was an emaciated, dehydrated-appearing boy of 9 years, apparently well oriented, although motor difficulties in speech made it impossible for him to reply to questions. He writhed about the bed with constant, irregular, arrhythmic, asymmetric movements.

Eyes: The pupils were equal and responded sluggishly to light. The eyes rolled about, seemingly as a part of the choreiform movements. Funduscopic examination showed severe optic neuritis and retinitis. There were no hemorrhages, exudate or choking.

Mouth: The lips seemed parched; the tongue was furred and dry.

Neck: Shotty lymphadenopathy was observed. The boy lay with his head retracted, and his neck offered firm resistance to flexion.

Chest: The breathing was vesicular but was "catchy," as though choreiform movements involved muscles of respiration.

Abdomen: No real rigidity was evident, but there were transitory waves of involuntary spasm, apparently part of the choreiform movements.

Skin: There was evidence of loss of weight; the skin was loose and wrinkled, displayed a dusky pallor and appeared greatly dehydrated. The palms and soles presented a horny, cornified desquamation. Over the entire body there were dusky brownish plaques, residuals of the eruption previously described.

Neurologic Examination.—The patient was confined to bed and was unable to sit or turn, because of lack of voluntary muscular control. There were constant choreiform movements involving the head, trunk and extremities. He experienced motor difficulties in swallowing, and speech was impossible. He was incontinent of urine and feces. He seemed well oriented and was pleasant and cooperative to the best of his ability.

From the Pediatrics Service of the Edward J. Meyer Memorial Hospital.

Reflexes: The knee jerks were active, and the Babinski sign was bilaterally positive. The cremasteric reflex was present, and the abdominal reflex was elicited. The Kernig and Brudzinski reflex reactions were positive.

Impression: The tentative diagnoses were: (1) postinfectious encephalitis; (2) dehydration; (3) malnutrition, and (4) faded dermatitis medicamentosa.

Laboratory Examination.—Blood count: Examination of the blood showed: hemoglobin content, 69 per cent; erythrocytes, 3,900,000, and leukocytes, 5,500, among which were 45 per cent segmented cells, 13 per cent stab cells, 22 per cent eosinophils and 18 per cent lymphocytes.

Urinalysis: The urine was yellow and acid and had a specific gravity of 1.025. It contained albumin (1 plus), rare pus cells and occasional crystals but no sugar or acetone.

Spinal Puncture: A spinal puncture, done on August 3, yielded 10 cc. of clear fluid under normal pressure. It gave a negative reaction for globulin and contained 1 white blood cell and 47 mg. of sugar per hundred cubic centimeters.

Wassermann Test of the Blood: The Wassermann reaction of the blood was negative.

Dehydration was combated by administering a 10 per cent solution of dextrose intravenously. The patient's general condition improved, but there was no change in his neurologic state except that he could swallow if fed slowly by dropper. On August 6 a determination of blood bromide was made (method of Wuth [1] as modified by Katzenelbogen and Czarski [2]). The blood bromide concentration was found to be 200 mg. per hundred cubic centimeters. Thus, in addition to the diagnoses previously made, it was felt that the picture was complicated by bromide poisoning. The child was given 150 grains (10 Gm.) of sodium chloride daily in divided doses of a 5 grain (0.32 Gm.) capsule every half-hour followed by a drink of water or fruit juice and was fed a high caloric liquid diet with a high salt content. Improvement accompanying the administration of sodium chloride was prompt and spectacular. On August 9 he could speak fairly well, tried to help himself and took fluids from a drinking tube. On August 10 he laughed and joked, preferred a tumbler to the drinking tube and was actively interested in helping record the fluid intake. He still had some nuchal rigidity. The oral mucosa was no longer dehydrated. The tongue protruded in the midline with a coarse tremor. Some facial weakness (right side) was apparent. Abdominal reflexes were present on the right but not on the left. A week later he looked much better; he still had some weakness of the right arm, and the biceps reflex was absent, but the flexors showed response. The left biceps reflex was normal. The neck was flaccid; the knee jerks were hyperactive. There was no Babinski reaction and no facial weakness or weakness of the circumorbital muscles. The abdominal and cremasteric reflexes were present and normal. Throughout his hospitalization there was evidence of mental disturbance, with frequent unmotivated screaming, irritability and excitement. On August 20 he left the hospital, able to sit and stand unaided. There were no choreiform movements. There was slight weakness of the supinator muscles of the right forearm and of the evertors of the right foot. He was no longer incontinent.

Blood bromide levels throughout his illness were: August 8, 200 mg. per hundred cubic centimeters of blood; August 11, 125 mg.; August 16, 75 mg.; August 20, 50 mg.; August 26, about 15 mg., and October 6, no trace. At home he improved steadily. One month later there was no evidence of muscular weakness or other abnormality, except that his temperament had changed from that of an easy-going, agreeable child to that of one who flew into rages without provocation. He had never done well in school, having attended three years without passing the first grade. When he returned to school after this illness, he was even less able to cope with the work. Throughout the following year the teacher found him unable to keep up with the class and subject to temper tantrums.

In April 1941, one year and eight months after the illness, there were no unusual physical or neurologic conditions. He was referred to the mental hygiene clinic of the Gowanda State Homeopathic Hospital for psychometric and psychiatric examinations. Dr. Henry D. Marritt, who examined the boy, reported a provisional diagnosis of mental deficiency (postencephalitic moron) and emotional instability and attributed the conditions to hereditary and postencephalitic causes. In his interpretation of the case Dr. Marritt stated: "It seems probable that the boy has been somewhat retarded since birth. How much the encephalitis is responsible for the

1. Wuth, O.: Rational Bromide Treatment: New Methods for Its Control, J. A. M. A. **88**:2013 (June 25) 1927.

2. Katzenelbogen, A., and Czarski, T.: Improved Colorimetric Method for Determination of Bromide Concentration in Blood and Cerebrospinal Fluid, Proc. Soc. Exper. Biol. & Med. **32**:136 (Oct.) 1934. Katzenelbogen, S., and Goldsmith, H.: The Hemato-Encephalic Barrier: The Diagnostic Value of the Bromide Test in Mental Diseases, Am. J. Psychiat. **10**:1045 (May) 1931. Stitt, E. R.; Clough, P. W., and Clough, M. C.: Practical Bacteriology, Haematology and Animal Parasitology, ed. 9, Philadelphia, P. Blackiston's Son & Co., 1938, p. 681.

retardation is difficult to say. Certainly the encephalitis seems to be responsible for the lack of emotional control, as the history has pretty well established that he had a normal disposition before his illness."

COMMENT

This case is interesting from three different angles: (1) postmeasles encephalitis, (2) postvaccinal aggravation and (3) bromide poisoning. It must be emphasized that the prostrating headaches began during convalescence from measles and prior to the administration of any medication. In view of later developments, it seems that the involvement of the central nervous system was first manifested at that time. Vaccination against smallpox undoubtedly aggravated the already existing condition. The process is regarded as postinfectious encephalitis, beginning as postmeasles encephalitis and aggravated by vaccination against smallpox. This diagnosis is based on the history of intense headaches and subsequent listlessness developing during the convalescence from measles, the typical ocular conditions [3] and the behavior disturbances which appeared. The normal spinal fluid is not incompatible with postinfectious encephalitis.[4]

Which part of the conditions were due to encephalitis and which to bromides given as treatment is difficult to say, but apparently at the late date I saw the boy bromide poisoning caused the main neurologic manifestations. This was suggested by the high blood bromide level and substantiated by the improvement following sodium chloride therapy and the resultant fall of the blood bromide level. I shall consider postmeasles encephalitis and postvaccinal encephalitis together, for they fall in the group of serious manifestations occasionally following or accompanying one of the infectious diseases, for which in 1872 Westphal suggested the name "acute disseminated encephalomyelitis."

Acute Disseminated Encephalomyelitis.—Modern observers feel that these sequelae are actually becoming more numerous. They have been observed in association with so-called virus diseases and following diseases ordinarily regarded as of bacterial origin. The same structural changes may follow inhalation of carbon monoxide, ingestion of a sulfonamide drug, or a burn or other exogenous trauma. Often spontaneous outbreaks appear suddenly in previously healthy persons.

The actual cause of active disseminated encephalomyelitis remains undetermined. Present day theories include the following:

1. The lesions are due to a dissemination of the virus of the antecedent disease, with resultant direct action on the central nervous system.

2. Encephalomyelitis is a separate disease due to a specific neurotropic virus, somehow empowered by the antecedent disease so that it attacks the nervous system.

3. Encephalomyelitis represents the result of allergic phenomena occasioned by the associated illness.[5]

4. In recent studies the primary change is represented as an alteration in the clotting mechanism of the blood, the alteration possibly being an aspect of allergy.

3. Heath, P.: Measles Encephalitis: A Clinical Report of Some Eye Findings, Am. J. Ophth. **15**:2 (Feb.) 1932.

4. Putnam, T. J.: Newer Conceptions of Postinfectious and Related Forms of Encephalitis, Bull. New York Acad. Med. **17**:337 (May) 1941; abstracted, Internat. M. Digest **39**:3 (July) 1941.

5. Rivers, T. M.: Encephalitis as a Complication or Sequel of Virus Diseases, J. A. M. A. **92**:14 (April 6) 1929. Finley, K. H.: Pathogenesis of Encephalitis Occurring with Vaccination, Variola and Measles, Arch. Neurol. & Psychiat. **39**:1047 (May) 1938.

The parenchymal reaction is said to be one which characteristically follows closure of small vessels in the central nervous system.[6]

The concept of a single causative agent for all these encephalitides is attractive. In the case under discussion the last two theories are appealing when considered in conjunction with Bridgeman's case,[6] in which meningitis complicated mumps in November 1934 and encephalitis complicated measles in the same patient in February 1936. The theories suggest a certain reasonableness as to how these two complications in the central nervous system occurred with two different virus diseases in the same child. The parallel which exists between that child's plight and that of our patient in whom involvement of the central nervous system seemed to be in response to the joint influence of measles and vaccination for smallpox is impressive.

Reported pathologic changes in various encephalitides have been similar, the characteristic lesion being perivascular demyelination. Usually a cuff of mononuclear cells, congestion and hemorrhages surround the blood vessels. Lesions may be in the cord or brain and may involve white and gray matter, those in the white matter usually being more extensive. There appears to be but little injury to nerve cells or axis-cylinders. The spinal fluid is seldom normal; it may contain from 10 to 2,000 cells, an increased protein content (up to 200 mg. per hundred cubic centimeters) and a normal amount of sugar, and it may perhaps show an alteration in the colloidal gold curve.

The clinical picture varies, depending on the severity of involvement and the portion of the nervous system attacked. There are often initial drowsiness, muscular rigidity, twitching and convulsions followed by stupor and usually accompanied by a rise in temperature. The stupor may pass off without residual symptoms or may be prolonged, with bizarre neurologic conditions revealed with returning consciousness. Spastic paralysis, ataxia, chorea and aphasias are common. Mental disturbances are usually present during convalescence. Prolonged toxic psychoses have been reported. Many patients show lesions of the spinal cord. These lesions are serious, and the symptoms usually take longer to clear up than those of cerebral origin. This is especially true of transverse myelitis, which may persist for months and not infrequently is permanent. Despite the alarming nature of the symptoms, recovery is often rapid and complete. There may be spastic paralysis, coarse tremors and mental deterioration, which last for months and may be permanent. Death may occur from the intensity of the encephalitis or from intercurrent infection. The mortality rate is probably about 10 per cent. Treatment is entirely symptomatic.

Postvaccinal Encephalomyelitis.—Within the past decade the subject of postvaccinal encephalomyelitis has aroused interest because of the increasing number of cases reported throughout the world. This complication does not seem to depend on the intensity of the reaction to the vaccine. It may follow primary vaccination or revaccination. Infants seem less susceptible than older children.[6] Pathologic conditions and symptoms are comparable to those seen in postmeasles encephalitis. The onset may occur from a few days to several weeks after vaccination, the commonest time being about eleven days after inoculation, when the reaction is at its height.[7] Postvaccinal encephalitis is generally regarded as the most serious of the postinfectious encephalitides, the mortality being about 50 per cent. In nonfatal attacks recovery, as a rule, is complete.

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6. Bridgeman, M. L.: Meningitis Complicating Mumps and Encephalitis Complicating Measles in the Same Child, Am. J. Dis. Child. **53**:804 (March) 1937.

7. Gorter, E.: Postvaccinal Encephalitis, J. A. M. A. **101**:1871 (Dec. 9) 1933; abstracted, Abt, I. A., and Abt, A. F.: Year Book of Pediatrics, Chicago, Year Book Publishers, Inc., 1934, pp. 205-210.

Prophylaxis: Since infants under 1 year of age seem less susceptible to the disease, vaccination should be carried out at this age when possible, and it has been recommended that vaccination be deferred at times when epidemic encephalitis or some other infectious disease is prevalent in the community.[8]

Bromide Poisoning.—Cases of bromide poisoning have been repeatedly reported during the last fifteen years, but reports of brominism in children under 13 years have been rare. Gralka[9] in 1924 reported bromide intoxication in a child, and Harris[10] and his associates reported 2 such cases in 1940. Most of the afflicted persons are adult psychiatric patients. Since bromides are usually prescribed for an already existing psychic or neurologic condition, the symptoms of intoxication may complicate the clinical picture or overshadow the underlying pathologic process.

Bromide poisoning was first reported by Huette[11] in 1850, about ten years after the introduction of the bromides as therapeutic agents. Only since the reports of Wile[12] in 1923 and Wuth[1] in 1927 has the syndrome been recognized frequently.

Normally the halogen content of the body is composed chiefly of chlorides and is fairly constant, owing to the body's ability to regulate chloride excretion, any diminution of intake being compensated by a decreased output. Bromides are eliminated more slowly than chlorides. Increased ingestion of chlorides hastens excretion of bromides, a fact which forms the basis of therapy of bromide intoxication. Low intake of chloride, dehydration and impaired excretion all increase retention of bromide. Bromide displaces chloride during periods of administration, and serious depletion of chloride may occur. The disturbance in chloride metabolism is important in intoxication. A 25 per cent replacement may cause symptoms of intoxication, and 40 per cent replacement has been known to be fatal. Higher levels[13] are reported but are usually fatal. There is no absolute correlation between the severity of poisoning and the level of bromide in the blood.[14] Many factors determine the level at which a patient will show intoxication. In patients with low intake of chloride or debilitating disease intoxication appears early.[15] The definite "toxic zone" has been placed at 150 to 200 mg. per hundred cubic centimeters, but mild nervous manifestations may appear at 50 mg. per hundred cubic centimeters.[16] Symptoms vary in different patients, depending on constitutional and personality factors. Any type of mental or neurologic disease may be simulated. The onset is insidious, the first symptoms representing an extension of the therapeutic sedative action, but as intoxication increases the patient becomes restless and excited, some-

8. Armstrong, C.: Post Vaccinational Encephalitis, with Special Reference to Prevention, Pub. Health Rep. **47**:30 (July 22) 1932.

9. Gralka, R.: Akute Massevergiftung mit Bromnatrium: Endemisch aufgetretene nichtinfectiöse Schlafsucht, Klin. Wchnschr. **3**:319 (Feb. 19) 1924; cited by Harris.[10]

10. Harris, L. E.: Bromide Intoxication, Am. J. Dis. Child. **59**:835 (April) 1940; abstracted, Abt, I. A., and Abt, A. F.: Year Book of Pediatrics, Chicago, Year Book Publishers, 1940, p. 498.

11. Huette: Recherches sur les propriétés physiologiques et thérapeutiques de bromure de potassium, Mém. Soc. de biol. **2**:19, 1850; cited by Harris.[10]

12. Wile, U. J.: Further Contributions to the Experimental Aspects of Iodid and Bromid Exanthems, Arch. Dermat. & Syph. **8**:407 (Sept.) 1923.

13. Wagner, C. P., and Bunbury, D. E.: Incidence of Bromide Intoxication Among Psychotic Patients, J. A. M. A. **95**:1725 (Dec. 6) 1930. Barbour, R. F.; Pilkington, F., and Sargant, W.: Bromide Intoxication, Brit. M. J. **2**:957 (Nov. 14) 1936.

14. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941, pp. 155-165.

15. Curran, F. J.: A Study of Fifty Cases of Bromide Psychosis, J. Nerv. & Ment. Dis. **88**:163 (Aug.) 1938.

16. Bromides in Medicine, editorial, J. A. M. A. **115**:937 (Sept. 14) 1940. Hazards of Bromidism in Proprietary and Uncontrolled Hypnotic Medication, report of the Council on Pharmacy and Chemistry, ibid. **115**:933 (Sept. 14) 1940.

times being in a state simulating alcoholic intoxication. This often leads to increased medication. Slurring speech, generalized tremor and pronounced ataxia develop. There may be hallucinations, difficulty in swallowing and inequality and sluggishness of the pupils. Superficial reflexes may be absent and deep reflexes diminished. The intoxication may progress to stupor or coma and death. Only 25 per cent of patients with brominism have cutaneous eruptions, a point which may lead one to overlook the diagnosis. There may be an eosinophilia (as in the case described). The diagnosis is confusing, but, fortunately, the bromide content of the blood can be determined. The urine may be free of bromides even in the presence of a high level of bromide in the blood.[15]

Treatment is replacement of the bromide ion by the chloride ion. Sodium chloride is given by mouth and parenterally. Since bromide is secreted in the gastric juice as hydrobromic acid, it may be desirable to do gastric lavage.[17] Bondurant and Campbell [18] showed that an extract of the adrenal cortex (eschatin) given in combination with sodium chloride facilitates excretion of bromide by restoring the normal physiologic level of chloride.

Mortality from bromide intoxication is probably less than 1 per cent. Recovery may require from one to six weeks.[16]

As so often happens in bromide poisoning, it is difficult to separate the symptoms of poisoning from those of the disorder for which the patient was receiving the medication. In this case the bromide probably accounted for many of the abnormal conditions, for the picture changed dramatically as the blood bromide level fell.

SUMMARY

Mild symptoms of postinfectious encephalomyelitis following measles developed in a 9 year old boy. At the time the symptoms began to subside he was vaccinated for smallpox. When the vaccinia reaction reached its height, there was a profound increase in encephalomyelitic signs and symptoms. The picture was further complicated by bromide poisoning, suggested by a high level of blood bromide and substantiated by the improvement which followed administration of sodium chloride and the resultant fall of the blood bromide level.

CONCLUSIONS

Cases of encephalomyelitis following infectious disease or vaccination have been reported with increasing frequency during recent years.

Measles and vaccination against smallpox have been conspicuous as the precursors of such encephalitis. This case is of particular interest because the involvement of the central nervous system followed measles and was shortly made worse by a vaccinia reaction.

Postvaccinal encephalitis is rare and does not necessitate curtailment of vaccination but demands care and judgment in carrying out the procedure. Children should be vaccinated early, since vaccinations in early childhood are less likely to be complicated. Vaccination is contraindicated for debilitated children, for all children in the presence of epidemics of diseases affecting the central nervous system, and when the patient, as in this case, already shows signs of involvement of the central nervous system.

The case is of further significance because of the complication of bromide poisoning.

462 Grider Street.

17. Nuti, G. N.: Psychoses from Bromide: Cases, Gior. di clin. med. **21**:1451 (Dec. 10) 1940; abstracted, J. A. M. A. **116**:2724 (June 14) 1941.

18. Bondurant, C. P., and Campbell, C.: Adrenal Cortex Extract in the Treatment of Bromide Eruption and Bromide Intoxication, J. A. M. A. **116**:100 (Jan. 11) 1941.

STONES IN THE URINARY BLADDER IN CHILDREN

DIAGNOSIS AND TREATMENT IN SEVEN CASES

RICHARD B. TUDOR, M.D.
DURHAM, N. C.

Because stones rarely occur in the urinary bladder in children, 7 cases are reported to stress the fact that they may be overlooked and to emphasize the signs and symptoms which they cause. The incidence in this country has varied from 0.066 per cent in the present series (7 patients among 10,650 children admitted to Duke Hospital from 1930 to 1942) to 1.63 per cent at the Mayo Clinic.[1] The age distribution of vesical calculus also varies: In America less than 2 per cent of the afflicted persons are children, while Thomson reported a childhood distribution of 25 per cent in China,[2] Noble found a 22 per cent distribution in children under 11 years of age in Thailand [3] and Assenfeldt, in his series in Austria, found a 77 per cent distribution in children.[4] The usual factors predisposing to formation of vesical stones in children are the same as in adults.[5] Perhaps a dietary deficiency or monotony plays a greater part in children than in adults. This may be the reason for the more frequent occurrence of stones in countries in which infant feeding is least advanced. Vesical calculus occurs twenty times more often in boys than in girls,[6] probably because of the relatively easy passage of small stones through the short and distensible female urethra.[7]

Urinary frequency, dysuria, pyuria and hematuria were the most common presenting complaints in our series, dysuria being present in every child (tables 1 and 2). The symptoms of bladder stone usually are acute and well marked. This is due to the extreme sensitiveness of the mucous membrane and the activity of the reflexes and in part to the pyramidal shape of the bladder, which causes the stone to gravitate to the trigone. Here it produces severe irritation and is frequently caught by the contracting muscular fibers, causing severe pain and sudden obstruction to the outflow of urine. Pain on urination is commonly the outstanding symptom. Patient 6, a 3 year old white boy, had periods of acute

From the Department of Pediatrics, Duke University School of Medicine, and Duke Hospital.

1. Crenshaw, J. L.: Vesical Calculus, J. A. M. A. **77**:1071 (Oct. 1) 1921. Pool, T. L.: Personal communication to the author. Hager, B. H., and Magath, T. B.: Formation of Vesical Calculi, J. A. M. A. **90**:266 (Jan. 28) 1928. Twinum, F. P.: Bladder Stone in the Early Days of the New York Hospital, Urol. & Cutan. Rev. **15**:373, 1941.

2. Thomson, J. O.: Urinary Calculus at Canton Hospital, Canton, China, Based upon 3,500 Operations, Surg., Gynec. & Obst. **32**:44, 1921.

3. Noble, T. P.: Vesical Calculus in Siam, Brit. J. Urol. **3**:14, 1931.

4. Assenfeldt, cited by Kelley.[6]

5. Bliss, A. R., Jr.; Livermore, G. R., and Prather, E. O., Jr.: Relation of Vitamin A and Vitamin D to Urinary Calculus Formation, J. Urol. **30**:639, 1933. Bottone, J. J.: A Pure Cystine Vesical Calculus in a Boy of Five Years of Age, Urol. & Cutan. Rev. **15**:54, 1934. Goldberg, L.: Vesical Calculus in Infancy, Arch. Pediat. **58**:271, 1941. Eusterman, G. B., and Wilber, D. L.: Clinical Features of Vitamin A Deficiency, J. A. M. A. **98**:2054 (June 11) 1932. Higgins, C. C.: Production and Solution of Urinary Calculi, ibid. **104**:1296 (April 13) 1935.

6. Kelley, S. W.: Surgical Diseases of Children, ed. 3, St. Louis, C. V. Mosby Company, 1929, vol. 2.

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retention alternating with periods in which he could urinate normally. In patient 5, also a boy of 3 years, the stream started and stopped involuntarily during urination. One 13 year old boy had attacks of dull aching pain in the region of the bladder. The other 4 boys complained mostly of pain on urination, and 1 of them had associated pain on defecation. Four of the patients had urinary frequency, while 3 were reported as holding the genitals during urination. The associated pain and tenesmus often caused the children to jump about and pull at the prepuce during urination, a symptom of diagnostic value.

TABLE 1.—*Vesical Stones in Children*

Patient	Frequency of Attacks	Characteristics of Attack	Diagnosis Made by X-Ray	Cystoscopic Examination	Treatment
1. W. M., 13 yr. white boy	4-7 days, every 4-6 wk.	Intermittent dull aching pain in bladder region	+	0	Suprapubic cystolithotomy
2. S. H., 9 yr. white girl	Continual, especially last 3 mo.	Dysuria, pyuria, hematuria and frequency	+	+	Suprapubic cystolithotomy
3. R. P., 15 mo. white girl	Intermittent, 9 mo.	Straining at urination, with passage of gravel	+	0	Suprapubic cystolithotomy
4. L. C., 4 yr. white boy	With each urination 2 min. to 2 hr., 1 yr.	Pain on urination associated with fine stream and phymosis	+	0	Suprapubic cystolithotomy
5. T. W., 3 yr. white boy	With each urination 30 min. to 1 hr., 17 mo.	Crying and straining, fine stream, frequent stops and starts of stream	+	0	Suprapubic cystolithotomy
6. D. H., 3 yr. white boy	Intermittent, 5 wk.	Acute retention alternating with periods of normal urination; frequent catheterization	+	+	Suprapubic cystolithotomy
7. J. K., 7 yr. white boy	With each urination, 1 yr.	Hematuria, dysuria and pain on defecation	+	+	Transurethral fulguration of congenital urethral valves and suprapubic cystolithotomy

TABLE 2.—*Complaints*

Patients	Frequency of Urination	Urgency	Dysuria	Nocturia	Pyuria	Hematuria	Holding Genitals	Phymosis
1	+	+	+	+	+	0	0	+
2	+	0	+	0	+	+	0	0
3	+	0	+	0	0	+	0	0
4	+	0	+	+	0	+	+	+
5	0	0	+	0	+	0	+	+
6	0	+	+	0	+	+	+	0
7	0	0	+	0	+	+	0	0

Patients 2 and 7 also had congenital urethral valves.
Patient 6 had hydronephrosis of the right kidney and pellagra.

Although the vesical stones in all of our 7 patients were visualized by x-ray, the roentgen diagnosis of stones in the bladder is not as certain as that of renal calculi.[8] According to Mombaerts,[9] 50 per cent of vesical stones are not shown on roentgen examination, while the proportion of renal stones not shown is only 1.2 per cent. For this reason, a roentgenogram which does not show a stone must not be taken as certain evidence of the absence of stone. As a cystogram made after injecting air often shows stones which are otherwise invisible, cystoscopy should be resorted to in all suspected cases in which the plain roentgenogram and the cystogram with injected air do not reveal the presence of stones.

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CUSHING'S SYNDROME IN CHILDREN

REVIEW OF THE LITERATURE AND REPORT OF A CASE

JASON E. FARBER, M.D.

FRANCIS J. GUSTINA, M.D.
AND
ANTHONY V. POSTOLOFF, M.D.
BUFFALO

It is generally believed that Cushing's syndrome rarely occurs in children (Haymaker and Anderson). However, from a survey of the available literature we were able to collect 26 cases of the disease with onset before the age of 16. We are also reporting a case of our own.

REPORT OF CASE

R. C., a white boy aged 15 years, was admitted to the Meyer Memorial Hospital on April 2, 1941, complaining of generalized weakness and a severe persistent backache. His symptoms began in July 1940, with a rapidly acquired obesity. Mild general malaise and fatigue after moderate exertion also occurred about this time, steadily increasing to profound

Fig. 1.—Photograph of the patient five years before onset of the illness.

generalized weakness. In November 1940 the patient suffered mild frequency of urination with nocturia. He also had frequent sore throats, blurring of vision and occasional frontal headaches at this time. In January 1941 edema of the feet was observed on several occasions. Shortly afterward, he was admitted to a hospital, where a diagnosis of hypothyroidism and chronic tonsillitis was made. A tonsillectomy was performed. He was readmitted to the same institution in March 1941 with complaints of generalized weakness and fatigue which had considerably increased in degree since his previous stay in the hospital.

His history of growth, development and illnesses was not remarkable, although he was considered mentally retarded. The family history was noncontributory.

Physical examination on admission revealed a well developed, obese white boy who was moderately dyspneic. He complained of severe low backache whenever a change in position was attempted and was unable to sit up because of his extreme general weakness as well as the pain associated with motion. The obesity was confined to the face, neck and trunk; the extremities were spared. He was 170 cm. in height and weighed 62.5 Kg. His face was florid, greasy and hairy, and there were a few small areas of telangiectasia. Examination of the eyes showed the optic disks to be normal. There was no evidence of papilledema, exudates or hemorrhages. The examination of the visual fields showed some mild peripheral contraction, more evident in the right eye. Red fields and blindspots were normal. Many of his teeth were carious. Examination of the heart and lungs disclosed no abnormalities. The blood pressure was 184 mm. of mercury systolic and 112 mm. diastolic. The external genitalia were

From the Edward J. Meyer Memorial Hospital and the University of Buffalo School of Medicine.

large but otherwise normal in appearance. There was considerable tenderness on pressure over the lumbar vertebrae. On the lateral and anterior surfaces of the thighs and flanks and to a lesser extent on the legs were many purplish striae cutis distensae (fig. 2). Neurologic examination was noncontributory except for revealing sluggish patellar and achilles reflexes. The results of several blood counts are shown in table 1.

Laboratory Data.—Chemical examination of the blood showed: urea, 9 mg. per hundred cubic centimeters; calcium, 11.3 and 9.7 mg.; phosphorus, 3.6 mg.; phosphatase, 5.5 Bodansky units; cholesterol, 106 and 164 mg. per hundred cubic centimeters; total serum protein 5.8 Gm. per hundred cubic centimeters; carbon dioxide–combining power of the plasma, 67.2 volumes per cent; chlorides, 391, 442 and 415 mg. per hundred cubic centimeters. The results of several dextrose tolerance tests are shown in table 2. The Wassermann and Kahn reactions of the blood were negative. Several examinations of the urine gave negative results. The phenolsulfonphthalein test indicated normal excretion, but the Mosenthal test of renal function revealed poor concentrating power. The basal metabolic rate was —3 per cent and —10 per cent on separate occasions. The spinal fluid contained 83 mg. of sugar and 485 mg. of chlorides per hundred cubic centimeters. Examination of sputum and a Mantoux test gave no indication of tuberculosis. A roentgenogram of the chest revealed no infiltration of the lungs, but the heart appeared slightly enlarged. The entire osseous system, especially the skull and spine, showed severe osteoporosis. The skull had a ground glass appearance, and the sella turcica was of normal size. All of the lumbar vertebrae showed narrowing of the bodies due to expansion of the nucleus pulposus.

Clinical Course.—The patient's course became progressively worse. He became more dyspneic, and his face grew more florid and obese (fig. 2), so that his eyes appeared nearly

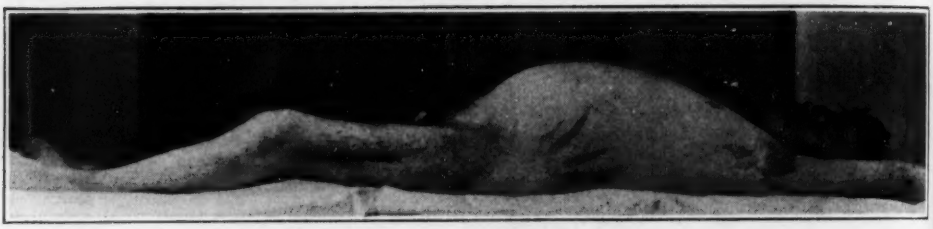

Fig. 2.—Photograph of the patient, prone position, lateral view.

TABLE 1.—*Serial Blood Counts*

	Hemoglobin (Sahli)	Red Cells	White Cells	Segmented Polymorphonuclears, %	Stabs, %	Lymphocytes, %	Monocytes, %	Eosinophils, %
4/ 4/41	118%	5,230,000	10,500	61	25	14		
4/12/41	113%	.....	11,850					
4/21/41	114%	4,950,000	14,450	83	4	10	3	
5/16/41	108%	5,350,000	12,250	71	8	15	5	1

TABLE 2.—*Results of Dextrose Tolerance Tests (Milligrams per Hundred Cubic Centimeters of Whole Blood)*

Date	Fasting	30 Min.	60 Min.	120 Min.	180 Min.
4/ 9/41	170	138	160	156	
4/16/41	94	142	167	156	106
5/ 9/41	112	220	234	306	
7/10/41	139	*250	340	260	

covered by the fatty rolls. He was soon unable to have penile erections. He was given a series of roentgen treatments to the pituitary gland but with no apparent benefit.

Throughout his residence at the hospital the temperature remained normal while the pulse rate ranged from 70 to 110 per minute. Blood pressure (taken daily) varied from 190 to

156 systolic and from 142 to 112 diastolic. Examination of the eyegrounds on July 21 showed evidence of prolonged papilledema with absence of disk margins and with many surrounding old hemorrhages and exudates and a few areas of retinitis proliferans. The visual fields showed beginning bitemporal hemianopsia.

Roentgen studies with diodrast as a contrast medium showed the circulatory function of the kidney to be normal. Retrograde pyelograms strongly suggested the possibility of a tumor in the region of the upper pole of the right kidney extrinsic to the organ. After the completion of these studies, a perirenal pneumoroentgenogram (fig. 4) was made. Both kidneys were well outlined. The upper pole of the right kidney was obscured by a large mass which was clearly delineated, measuring 8 by 8 cm. in diameter and situated in the anatomic position of the adrenal gland.

Fig. 3.—Photograph of the patient. Note the plethoric facies with hirsuties.

A roentgenogram of the chest at this time showed scattered areas of pulmonary infiltration suggesting metastases of the tumor. In spite of this it was deemed advisable to remove the mass previously outlined, and through a lumbar incision a large adrenal tumor (fig. 5) was removed. The patient died the following day. An autopsy was performed.

Autopsy.—The body was that of a 15 year old boy with a pronounced "Buffalo" type of obesity. The face exhibited hirsutism. Silvery purplish striations were found over the anterior axillary folds, the lower part of the abdomen and the thighs and flanks. A recent nephrectomy incision was found over the right loin. The external genitalia were hyperplastic.

Head: The calvarium was thicker than normal. The brain weighed 1,310 Gm. and was symmetric both externally and on section. The pituitary gland was attached by a thin stalk measuring 3 mm. in length, and the gland measured 5 by 4 by 4 mm. There was no gross evidence of adenoma. The pineal body measured 5 by 4 mm., and a cyst 1 mm. in diameter was found in its center. The clinoid processes showed no evidence of expansion.

Neck: The lobes of the thyroid gland were symmetric and measured 6 by 2.5 by 2.5 cm. On section the gland was homogeneously pink and moderately firm. The follicular pattern was maintained grossly.

Chest: The right lung weighed 540 Gm. and the left 410 Gm. Numerous subpleural nodules of varying sizes were found. The largest of these measured 2 cm. and the smallest 2 mm. in diameter. These nodules were firm, rounded and yellow-brown. The parenchyma surrounding these nodules was atelectatic. The pericardium and myocardium were diffusely infiltrated with fat. The left ventricular wall measured 2 cm. and the right 0.5 cm. in thickness. The thymus was not found.

Abdomen: The abdominal organs were infiltrated with fatty tissue, particularly the liver, pancreas, mesentery and omentum. The organs weighed as follows: the liver, 2,350 Gm.; the pancreas, 110 Gm., and the spleen, 290 Gm. The left adrenal gland was atrophied and compressed, measuring 0.2 to 0.4 by 3 by 1.5 cm. The cortex was thin, well defined and yellow.

Fig. 4.—Roentgenogram of the tumor after perirenal insufflation of air.

Exploration of the surgical incision in the right loin revealed a pocket measuring 10 by 15 by 6 cm., packed with strips of gauze. The tumor mass evidently had covered the upper two thirds of the right kidney. The wall of this pocket was rough and granular, and remnants of tumor masses, 2 to 3 cm. in diameter, were found. These were yellow-gray and firm. The surface of the right kidney was smooth, and the kidney and capsule were intact. The cortex of each kidney measured 6 to 7 mm. in thickness. Further dissection revealed an extension of the tumor into the right adrenal vein projecting up and into the lumen of the inferior vena cava and causing almost complete obstruction. The mass was firm and brownish yellow.

The testicles measured 6 by 2.5 by 2.5 cm. and were of moderate consistency.

Gross Description of the Tumor: The tumor was brown, lobulated, nodular, partially encapsulated and firm. It weighed 530 Gm. and measured 22 by 15 by 7 cm. On section the nodules ranged from 5 mm. to 4 cm. in diameter.

Histologic Examination.—Tumor: There were numerous polyhedral cells arranged in cords and ovoid groups, many of these perivascular in arrangement. The cytoplasm of the cells was light staining. The nuclei were large, vesicular, deep staining and centrally located and

showed hyperchromatism and numerous mitotic figures. Invasion of the capsule of the tumor was noted. Necrosis and hemorrhage were pronounced. Sections stained by the Wiesel method showed no chromaffin tissue. The tumor was identified as a cortical cell carcinoma.

Pituitary Gland: There was a slight preponderance of acidophilic cells in the pars anterior but no adenomatous formation. The cytoplasm of most of the basophil cells stained a homogeneous clear light blue with Mallory's aniline blue–acid fuchsin method and contained only a few granules. Various-sized vacuoles were scattered throughout. The nuclei appeared vesicular or round with no evidence of degeneration. No normal "ripe" basophils were seen.

Pineal Gland: The pineal gland showed the characteristic retrogressive changes which follow puberty. A simple involution cyst was noted.

Thyroid: There was an increased amount of connective tissue in the thyroid gland.

Lungs: The lungs showed considerable edema, and the tumor nodules appeared identical with the adrenal tumor.

Heart: The muscle of the heart was infiltrated with fat.

Liver: The liver showed fatty infiltration and some congestion and necrosis of the central vein.

Fig. 5.—Photograph of the adrenal tumor.

Spleen, Pancreas, Stomach, Intestines and Prostate: These organs were essentially normal.

Kidneys: The arterioles and capillaries of the kidneys showed slight hyaline thickening; the tubules showed a cloudy swelling. An occasional hypertrophied juxtaglomerular apparatus was noted.

Testicles: The testicles showed active spermatogenesis and an increased amount of interstitial tissue.

COMMENT AND REVIEW OF THE LITERATURE

In the years since Harvey Cushing's description of the syndrome bearing his name, a wealth of pertinent literature has accumulated. Cushing's evidence that the pituitary gland was chiefly responsible for the disease has been both supported and questioned. As a matter of fact, it is now well established that lesions other than a basophilic adenoma of the pituitary may also produce the syndrome. Chief of these are lesions of the adrenal cortex, both hyperplasia (Kepler, Kennedy, Davis and Walters) and tumor (Silver), various pituitary tumors including chromophobe (Fuller and Russell), and acidophil tumors (Horneck) and tumors of the

pars intermedia (MacCallum and associates), the ovarian tumors arrhenoblastoma (Dorfman, Wilson and Peters), teratoma (Krönke and Parade) and granulosa cell tumor (Haymaker and Anderson), and a thymic tumor (Leyton). What is more, in some instances (Bauer and Hall, Kellett and Stephensen) no demonstrable lesion could be disclosed. That so remarkable an entity can occur when the primary lesion is located in different organs of the body has stimulated both interest and study. Some investigators (Bauer) feel that Cushing's syndrome is primarily adrenal with secondary changes in the pituitary. In Oppenheimer's (Oppenheimer, Globus, Silver and Shoskan) analysis of the literature he found 6 cases of the syndrome with no evidence of basophilic adenoma. Contrariwise, in a series of 24 cases of basophilic adenoma of the pituitary both the syndrome and adrenal changes were absent. Regardless of the nature or location of the primary lesion, Crooke noted a characteristic hyaline change in the basophilic pituitary cells. The normal cytoplasm with basophilic granules was replaced by a dense homogeneous hyaline cytoplasm which stained a uniform grayish-blue with acid fuchsin and aniline blue. The hyalin, Crooke suggested, was an alteration in physiologic activity, not a parenchymatous degeneration in the ordinary sense. This conspicuous amount of hyaline change was the only abnormality common to all 12 of the cases studied and was therefore considered of fundamental significance. Rasmussen commented that these histologic changes in the basophils appear to be the most constant hypophysial change so far discovered.

In a thorough and analytic review Haymaker and Anderson presented a rational view of the syndrome. They pictured Cushing's disease as a form of an adrenocortical syndrome, another phase of which is the adrenogenital syndrome (*syndrome génito-surrénal* of Gallais) in which precocious maturity and the tendency to sex reversal are the chief features. The latter syndrome arises from alteration in function of the adrenal cortex. According to their conception Cushing's syndrome, characterized by specific obesity, hypertension, integumental changes, sexual depression, osteoporosis etc., is due to hypersecretion of adrenal cortex hormone, thus diametrically the opposite of Addison's disease "in the same sense that Grave's disease and Gull's disease are opposites." This intriguing hypothesis is worthy of further investigation.

The present study includes a review of cases of Cushing's syndrome in children with a report of a case of our own. It appears that when the syndrome develops in children the clinical picture eventually assumes a form identical with that in adults. The chief feature in the evolution of the disease in children seems to be the premature appearance of puberty and adolescence, i. e., precocious development of the genital organs, early menarche and early appearance of the secondary sex characteristics (Cushing; Gravano; Grupper). In other words, in at least its sexual aspects the child with full-blown Cushing's disease has become an adult. When this state of sexual maturity has been attained, the sexual dystrophy characteristic of adults with the disease e. g. amenorrhea in girls and impotence in boys, then occurs apparently regardless of the chronologic age of the subject. One is impressed, too, by the way in which the disease definitely ages all victims of it, as witnessed by photographs of patients with the disease.

In regard to this premature sexual maturity, Cushing noted that this feature appeared to characterize the disorder in children of either sex. One need only to refer to some of his original cases to verify this. For example, in his case 4 (table 3) he described a girl on whose face, axillas and pubes at the age of 11 years hair began to grow. This patient appeared many years older than her actual age. Case 6 is that of a girl who began to menstruate at age 9. In case 7 the patient began to menstruate at 10 years of age, when she acquired secondary sex char-

TABLE 3.—*Review of the Literature on Cushing's Syndrome in Children*

Series No.	Year Reported	Authors	Age of Patient	Age at Onset	Sex	Specific Obesity	Hypertension	Osteoporosis	Sexual Dystrophy	Hypertrichosis	Lineae Atrophicae	Polycythemia	Plethoric Facies	Weakness and Fatigue	Spinal Pain	Pathologic Condition and Comments
1	1913	Bauer and Wassing	16	15	M	+	+	+	+	+	+	..	+	..	..	Large testicles; basophil adenoma at autopsy
2	1919	Reichmann	36	15?	F	?	+	+	+	+	?	..	..	+	..	Obesity on face only; died following adrenalectomy; eosinophilic adenoma and hypertrophy of adrenal cortex
3	1921	Friedman	19	10	M	+	+	+	+	+	+	—	+	..	+	Glycosuria, hyperglycemia and hypercholesterolemia; no autopsy
4	1924	Oppenheimer and Fishberg	12	6	F	+	+	+	+	+	+	—	+	..	..	Hirsuties of face, axillas and pubes at age of 11; glycosuria; no autopsy
5	1927	Caussade, Abel and Michon	15	14	F	+	+	+	+	+	+	..	+	..	..	Diagnosed as endocrine obesity in 1927
6	1931	Teel	20	15	F	+	?	?	+	+	?	?	?	+	..	Menarche at age of 9; autopsy revealed basophil pituitary adenoma and enlarged adrenals
7	1932	Cushing (case 15)	15	8	F	+	+	+	+	+	+	..	+	..	..	Menarche at age of 10; low tolerance for sugar; glycosuria; increased calcium elimination; radiation of pituitary with improvement
8	1932	Bishop and Close	22	15	F	+	+	+	+	+	?	..	..	..	..	Basophil adenoma of the pituitary
9	1932	Ellis	12	10	F	+	+	—	+	+	+	—	+	..	..	Sexual maturity at 12; exploratory laparotomy did not reveal adrenal tumor
10	1934	Leyton	11	11	M	+	—	—	+	+	—	—	+	..	..	Hyperglycemia and glycosuria; at autopsy: carcinoma of thymus, adrenal cortex enlarged, pituitary normal
11	1934	Hoyle and Wall	18	15	F	+	+	—	+	+	+	+	+	..	..	Amenorrhea, mental depression and headaches; radiation of pituitary with possibly slight improvement
12	1934	Jamin	15	14	M	+	+	+	+	+	+	+	+	+	+	Typical case (photographs included)
13	1934	Kepler et al. (case 3)	9	4	F	+	+	—	+	+	+	—	?	..	..	Adrenal cortical adenoma removed; improvement
14	1935	Wright	11	10	F	+	+	+	+	+	+	+	+	+	+	At autopsy: adenoma hypophysis
15	1935	Lloyd	16	14	F	+	+	?	+	+	+	+	+	..	..	Headaches; no osseous changes
16	1936	Freyberg et al.	19	12	M	+	+	+	+	+	+	+	+	..	..	Basophil (?) adenoma of the pituitary; hyperplasia of the thymus
17	1936	Rasmussen	13	..	M	+	+	+	+	+	+	..	+	..	..	At autopsy: carcinoma of the adrenals; Crooke cells in the pituitary
18	1937	Lawrence	14	13	M	+	+	+	+	+	+	+	+	..	..	Hyperglycemia; at autopsy: adrenal hypertrophy and adenoma of the pituitary
19	1937	Sorkin and Vilkomirskiy (case 1)	19	14	F	+	+	+	+	+	+	+	+	+	+	Typical case (with photograph)
20	1937	Sorkin and Vilkomirskiy (case 3)	9	7	M	+	+	+	+	+	+	+	+	..	..	Impaired tolerance for carbohydrate
21	1937	Shoykhet and Palchevskiy	17	15?	M	+	+	+	+	+	+	+	+	..	..	Hyperglycemia and hypercalcemia; at autopsy: basophil pituitary adenoma, lipoidosis of parathyroids, changes in cells adrenal cortex, hyaline changes in vessels of all organs
22	1939	Loyani et al.	19	15	F	+	+	?	+	+	+	+	+	+	..	Radiation of pituitary with improvement
23	1939	Lefebvre	12	9	F	+	+	+	+	+	+	+	+	..	..	Onset following mumps
24	1939	Crooke (case 2)	6	6	F	+	+	—	+	+	+	—	+	..	..	Autopsy: carcinoma of adrenal cortex, hyaline changes in basophil cells of pituitary
25	1939	Crooke (case 3)	12	11	F	+	+	—	+	+	+	—	+	..	+	No adrenal tumor found on exploratory laparotomy
26	1941	Lintz	15	12	F	+	+	+	+	+	+	+	—	+	+	Low tolerance for sugar; hypercholesterolemia
27	1942	Present case	15	14	M	+	+	+	+	+	+	+	+	+	+	Typical case; at autopsy: adrenal cortical carcinoma; hyaline changes in basophil cells of pituitary as reported by Crooke

acteristics. The patient in case 9, a girl of 12 years of age, first came under observation owing to the early appearance of the secondary characters of sex.

The literature contains a number of reports of cases of the syndrome in children which do not fit precisely into the classic description of Cushing's syndrome and hence cannot be regarded as typical. For example, in the 3 cases of Pardee the patients had a uniformly distributed obesity although they had hypertension and other features of the syndrome. Cushing himself did not consider these typical cases, although it must be admitted that similarities were otherwise present. Gareiso, Schere and Pellerano in Argentina reported the case of a 14 year old girl with practically all the characteristic features except that the obesity was fairly evenly distributed. Massobrio and Boccuzzi wrote of a girl aged 17 years with symptoms dating from 1 year of age, chiefly plethoric obesity, precocious puberty, hypertrichosis and striae atrophicae, which they believe were due to a pineal tumor. The obesity was not of the characteristic distribution. There is some question in our minds about the case of Leyton. His patient, a boy of 11 years, became rapidly obese after an appendectomy; convulsions developed, and he died. There was no hypertension, no changes in the bones and apparently no lineae atrophicae. At autopsy a thymic carcinoma was found. The patient of Reichmann had certain atypical features, although the case was listed by Cushing as a verified case of basophilism. The obesity was confined to the face only and hence was not typical in distribution, and the protuberant eyes in addition to the loss of weight do not seem to belong to the accepted clinical picture. The patient however, had hypertension, osteoporosis, glycosuria and a plethoric facies.

Dunn reported the case of a woman aged 23 with menarche at the age of 9 followed by frequent prolonged menses and cessation of growth. At 13 years polyuria and nocturia occurred. At the age of 17 headache, weakness and suffocative attacks began, and soon after there was a rapid gain in weight. Eventually the characteristic clinical picture appeared, but relief followed the administration of massive doses of progynon B (alpha estradiol benzoate in oil). This therapy was based on Dunn's belief that a majority of the symptoms in basophilism are hypogonadal.

Hommes' case (not listed in our table) was that of a woman aged 22 years who was noticed to have the specific obesity characteristic of the syndrome by the age of 16, which suggested that the onset of the condition had probably been before that age. At autopsy a fibroadenoma (nonbasophilic) of the hypophysis was found. The other endocrine glands were not pathologically altered.

Russell, Evans and Crooke described a woman of 33 who exhibited a generalized obesity dating from early childhood but had no change in catamenia. The authors admitted that her condition was not typical of the syndrome. Goldberg reported the case of a 12 year old girl with a pituitary syndrome characterized by a rapidly acquired but generalized obesity at the age of 9, a moderate but not persistent vascular hypertension and precocious adolescence followed by amenorrhea. There was no hypertrichosis or purplish striae, and, as the author noted, the condition was not typical of Cushing's entity. The case resembled, however, in certain respects the cases of Pardee.

In table 3 are listed, including our own, 27 cases of the syndrome with onset before the age of 16. There were 17 girls and 10 boys. The earliest onset was at the age of 4 years. In these cases the condition seems to correspond to Cushing's original description. While the available literature has been surveyed, we feel that there are probably some cases of the syndrome described under other names published before 1932 that were not located. The column in table 3 entitled "Sexual Dystrophy" refers especially to premature puberty and adolescence with onset of

catamenia, usually followed later by amenorrhea in females and impotence in males. We did not find a case of the syndrome in a Negro child. In 12 of the cases there was an autopsy; in 4 others there was surgical exploration. Four patients received irradiation, with stated improvement of 3 of them. In 8 patients an adenoma of the pituitary gland was found; in 4, a tumor of the adrenal cortex; in 4, adrenal hypertrophy, and in 1, a thymic tumor.

In the case being reported the condition conforms in entirety with Cushing's original and classic description of so-called pituitary basophilism. For here is the peculiarly distributed "buffalo" type of obesity, the plethoric hairy facies, the hypertension and purplish abdominal striae, the sexual dystrophy, the generalized osteoporosis and the backache and weakness. Our case conforms to the group of cases of adrenal involvement without pituitary adenoma, but the basophil cells rather strikingly exhibited the characteristic hyaline changes described by Crooke. Morphologically, the tumor was a carcinoma of the adrenal cortex. Wiesel's bichromate stain showed absence of any chromaffin tissue, which ruled out a tumor originating in that type of tissue. Laboratory studies showed a decreased tolerance for dextrose. The serum cholesterol level was somewhat low on one determination but normal on a second. The protein and the chloride content of the serum were low. The calcium and phosphorus levels of the serum were normal; the potassium level was not determined. The low level of proteins in the blood conforms with Albright's conception that many of the clinical manifestations of the syndrome are the result of lack of protein. The phosphatase activity of the blood was normal. Unfortunately, we were unable to make an examination of the urine for androgens, e. g. the 17-keto steroids. Such a determination would probably have permitted differentiation between an adrenal and a pituitary origin for the disease, the presence of these substances arguing strongly in favor of an adrenal lesion (Dorfman, Wilson and Peters).

The entire skeletal system showed definite osteoporosis with structural alterations in the vertebral bodies evidently following decalcification. The skull was particularly osteoporotic. Serial blood counts showed a high value for hemoglobin and a high normal red cell count. The hypertension persisted, and there were hemorrhages in the ocular fundi. A large adrenal tumor was outlined by means of perirenal pneumoroentgenograms. Unfortunately, the tumor was highly malignant and metastasized rapidly. At autopsy metastases of the tumor were found in the lungs, the left kidney, the adrenal vein and the inferior vena cava.

SUMMARY

The literature on Cushing's syndrome in children is reviewed, and a case is reported. The disease in children seems to be characterized by premature sexual maturity. The patient, a white boy of 15 years, exhibited the typical "buffalo" type of obesity, hypertension, plethoric facies with hypertrichosis, purplish striae distensae, sexual precocity, generalized osteoporosis, weakness and backache. Laboratory studies showed a decreased tolerance for sugar, hypoproteinemia and hypochloremia. Perirenal pneumoroentgenograms outlined a large adrenal tumor, which was then removed. The tumor was an adrenal cortical carcinoma. Death ensued, and at autopsy metastases of the tumor were found in the lungs, kidneys and veins. The basophil cells of the hypophysis showed the hyaline changes described by Crooke.

Dr. W. F. Jacobs and R. A. Sloan assisted in the pathologic study, and Miss Phyllis Hubbard aided in the bibliographic work.

462 Grider Street.

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Progress in Pediatrics

TUMORS OF THE BRAIN IN CHILDREN AND IN ADOLESCENTS

A CLINICAL AND ANATOMIC SURVEY OF NINETY-TWO VERIFIED CASES

JOSEPH H. GLOBUS, M.D.
NEW YORK

LIEUTENANT JOSEPH M. ZUCKER*
MEDICAL CORPS, ARMY OF THE UNITED STATES
AND
JOSEPH M. RUBINSTEIN, M.D.
ALTON, ILL.

A relatively large number of instances of tumor of the brain in children have come under clinical and anatomic investigation at the Mount Sinai Hospital in the course of the last twenty years. While highly important studies on similar material have been made by a number of other observers,[1] it seems advisable to place on record additional material, particularly that which was carefully studied over a long period. The time element is considered important, for it is thought likely to reveal some instructive clinical and anatomic observations. The latter are centered mainly about such questions as the type of tumor commonly encountered in children, the ages at which tumors of certain types are more likely to occur, the existence or absence of characteristic clinical manifestations of tumor in the young and, finally, the benefits derived from surgical intervention or radiotherapy as measured by comparing the survival periods of patients with tumor of the brain with and without surgical intervention.

MATERIAL: TYPES AND FREQUENT SITES OF TUMOR ENCOUNTERED IN CHILDREN

The material used for this study consists of a total number of 92 cases in which tumor of the brain was found in children from 1 to 16 years of age. In taking 16 years as the highest age limit for this group, the advice of pediatricians and the precedent set by Bailey, Buchanan and Bucy [1d] were followed. In cases in which death occurred without surgical intervention, the diagnosis was confirmed by necropsy, while in those in which the patient survived operation the diagnosis was made by biopsy. In some instances both biopsy and necropsy diagnoses were

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From the Division of Laboratories, the Neurologic and the Pediatric Services of the Mount Sinai Hospital.

*Former Moritz Rosenthal Fellow in Neuropathology, the Mount Sinai Hospital.

1. (*a*) Cushing, H.: Intracranial Tumors, Springfield, Ill., Charles C Thomas, Publisher, 1932, p. 150. (*b*) Zülch, K. J.: Die Hirngeschwülste des Jugendalters, Ztschr. f. d. ges. Neurol. u. Psychiat. **161**:183, 1938. (*c*) Stern, R. O.: Cerebral Tumors in Children: A Pathologic Report, Arch. Dis. Childhood **12**:291, 1937. (*d*) Bailey, P.; Buchanan, D. N., and Bucy, P. C.: Intracranial Tumors in Infancy, Chicago, University of Chicago Press, 1939. (*e*) Marburg, O.: Some Remarks on Tumors of the Brain in Childhood, J. Nerv. & Ment. Dis. **4**:446, 1942.

available. Not without significance is the fact that in none of the cases without operation has the patient survived, while in 20 of those with craniotomy the patient is still living (table 1).

The types of tumor prevalent among children differ in some respects from those encountered in older age groups. This is particularly true of the frequency with which some types of tumor are more likely to be found in the younger groups and the rarity with which other types of tumor are found in the same age group (table 2).

It will be noted that the autochthonous blastomatous forms of tumor, such as pinealomas and craniopharyngiomas, on one hand, and those tumors which are

TABLE 1.—*Total Number of Children with Verified Tumors of the Brain (92)*

Status of Patient	Type of Treatment		
	Craniotomy	Minor Surgical Measures	No Surgical Intervention
Living	20	0	0
Dead	43	10*	19†

* Minor surgical measures included: exploratory trephine, 1 case; ventricular puncture, 4 cases; ventriculography, 5 cases.
† None of these children had hemangiomas.

TABLE 2.—*Tumors of the Brain in Children and Adolescents Distributed According to Type*

Type of Tumor	Status of Patient	
	Dead	Living
Hemangioma (cerebellar, 9; cerebral, 2)	1	10
Medulloblastoma	9	0
Pinealoma	9	0
Craniopharyngioma	6	3
Spongioneuroblastoma	7	1
Glioma and glioneuroma (transitional)	8	0
Ependymoma	7	0
Tuberous sclerosis	4	2
Spongioblastoma multiforme	5	0
Sarcomatous meningioma	5	0
Gliogenous cyst	1	2
Metastatic growth	3	0
Infundibuloma	2	0
Schwannoma (central neurinoma)*	0	3
Pial meningioma	2	0
Unclassified	2	0
	72	20

* One associated with tuberous sclerosis.

best defined as massive heterotopias (embryonal displacements), such as hemangiomas, medulloblastomas, ependymomas and the tumors in tuberous sclerosis, on the other hand, constitute a large proportion (more than half) of the tumors here reported. The remainder of the neoplasms in this series is made up of a large assortment of tumors, and they as well as the foregoing types will be discussed in greater detail as the illustrative material is presented.

This departure exhibited by the greater prevalence of certain types of tumors found in children is paralleled by another deviation: a certain predilective localization of tumors in children and adolescents. In this age group the tendency is for a preferential situation of the expanding lesion in the posterior fossa as shown by the fact that in 55 of 86 of the cases studied the growth was infratentorial in location. (We have excluded 6 cases of the entire group because in them by their nature, being metastatic or disseminated, the lesions were multiple.)

HEMANGIOMA (HEMANGIOENDOTHELIOMA)

The first 2 cases to be presented are selected from the cases of hemangioma, because they serve well to illustrate the tumor most frequently encountered among children. They are of particular interest because they are instances of a benign blastomatous lesion which may be regarded as predominantly selective for the cerebellum. This is a significant feature, for it places this type of tumor among similar blastomatous vascular cerebellar lesions of the type described by Landau.[2] In the latter, however, the vascular tumor of the cerebellum is usually accompanied by vascular malformations in the retina and, at times, in other organs.

The histologic character of the tumor, because of the presence of a large number of glial elements, is often misinterpreted, and the neoplasm is not infrequently erroneously diagnosed as astrocytoma or gliogenous cyst. The cases constituting this group offer an excellent opportunity to study this problem. The conclusion is reached that the glial components of such a tumor do not represent their basic histologic elements but are little more than the expression of a normal reaction, characteristic of glia cells whenever they are brought in contact with a vascular structure.

From the clinical point of view, it may be said that the location of the tumor is usually roughly indicated by the presence of signs and symptoms of an expanding intracranial lesion and by the dominating cerebellar manifestations. It is most gratifying to report that the behavior of these tumors is usually benign, as shown by this group of 11 cases, in only 1 of which was there a fatal issue. But even in that instance, had it not been for an unfortunate secondary infection, the young patient would have joined the other 10 in recovery. The latter are living, having survived surgical intervention for periods varying from one to eight years.

CASE 1.—*Hemangioendothelioma of the cerebellum; repeated craniotomies in the course of nine years, with ultimate sustained recovery for eight years.*

History.—M. Mc., a girl aged 5 years at the time of her first admission to the hospital (Nov. 11, 1925), had been subject to recurrent headaches for a period of four months and had vomited repeatedly for about two months. At the time of admission examination of the fundi disclosed bilateral papilledema of 1½ diopters. Her head tilted to the right, and she showed mild signs referable to the cerebellum. The diagnosis of a neoplasm in the posterior fossa was made, and a suboccipital craniotomy revealed what was reported by the surgeon to be a "typical gliomatous cyst" in the right cerebellar hemisphere. It was emptied, and the subsequent high voltage roentgen therapy was followed by marked relief from her symptoms. One year later (Jan. 24, 1927) the child was brought back to the hospital because of recurrence of the vomiting, reappearance of weakness in both legs and a staggering gait with a tendency to fall to the right of four months' duration. Another craniotomy was then performed, and the "cystic glioma" was again evacuated and cauterized with Zenker's solution. She again did well, becoming free of most of her symptoms except ataxia, right cerebellar signs and a central weakness of the right side of the face, which persisted. In the course of the next six years she was given several series of high voltage roentgen treatments. At the end of that period (1933) she again began to complain of headaches and dizzy spells and would occasionally vomit. She reentered the hospital on April 19, 1934. At that time the following significant findings were recorded: bilateral secondary atrophy of the optic nerve with marked impairment of vision, on the left more than on the right; a left temporal defect in the visual fields; right central facial weakness; bilateral patellar and ankle clonus with a bilateral Babinski sign; wide-based gait and a tendency to sway backward, and bilateral ataxia on finger to nose and heel to knee tests, more pronounced on the right side. Reexploration (on April 26) revealed a large cyst at the site of the previous operation. It was again emptied, but at this operation part of its wall and several small pieces of tumor were removed.

Pathologic Examination of the Surgical Specimen.—There were four pieces of tumor. Several of these pieces presented a smooth lining on one edge resembling the wall of a cyst.

2. Landau, A. I.: Studien über Kleinhirncysten, Acta path. et microbiol. Scandinav. (supp.) **1**:1, 1926.

Sections displayed fields with fairly solid cell formation surrounded by a stroma of connective tissue containing many blood vessels (fig. 1) and an occasional hemorrhage. There were also fields of loose cellular makeup in which the cells were vacuolated and gave rise to many cytoplasmic processes. Gold and silver stains revealed an occasional glia cell in the looser tissue. It is conceivable that the dense areas were due to scar formation from the previous operation, but the other area had the appearance of a hemangiomatous tumor.

Follow-up.—The patient was seen repeatedly at the follow-up clinic. At the most recent examination, April 1, 1941, she was reported to manifest mild cerebellar signs but to have retained all her gains and to be otherwise symptom free.

Comment.—Of clinical significance in this case is the fact that the patient had maintained an unaltered condition for eight years after the last operation, and, aside from the intercurrent neurologic manifestations, due to filling of the cyst, for the first two years, she had lost no ground for almost seventeen years since

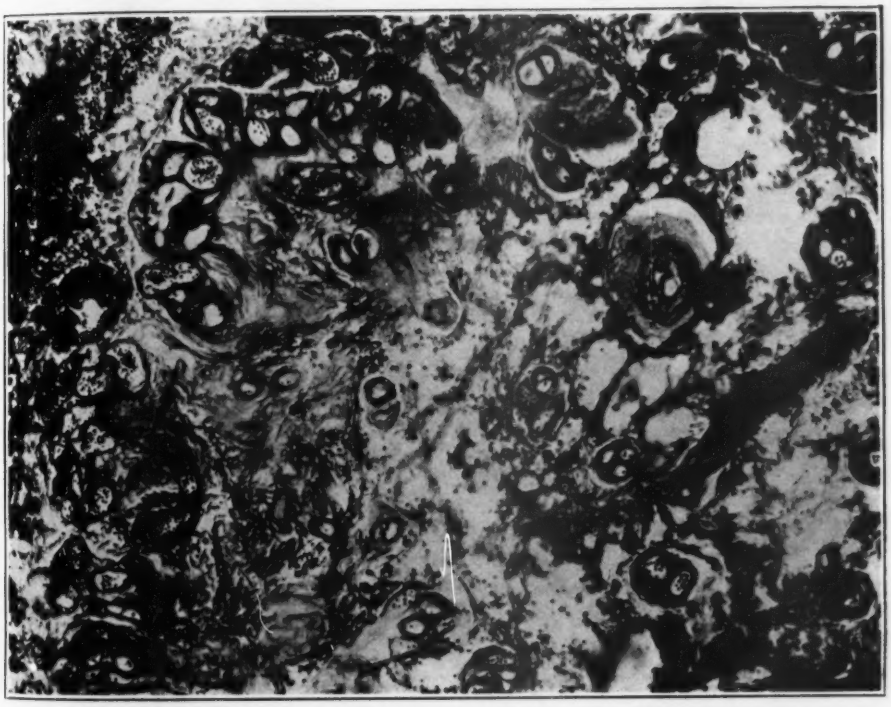

Fig. 1 (case 1).—Section exhibiting the hemangiomatous character of the tumor. Van Gieson stain; × 200.

the first craniotomy. The benign clinical course is in full accord with the histologic character of the tumor. Not infrequently, as indicated by the neurosurgeon's reference to the tumor as a "typical gliogenous cyst," these cystic hemangiomas are misidentified. This in all probability is due to the presence in such tumors of a fairly large number of fibroblastic glial cells. However, it is not realized that this glial proliferation is a reaction which is characteristically displayed by glia under normal circumstances in the proximity of blood vessels. Thus, wherever vessels are in large aggregations, as in a vascular tumor, it is not surprising to find large accumulations of glia, without the basic hemangiomatous character of the tumor being necessarily altered.

CASE 2.—*Hemangioendothelioma of the cerebellum; craniotomy followed by secondary infection and death; necropsy.*

History.—R. S., a girl aged 11 years, was apparently well until seven months before admission to the hospital, when it first was noted that she had a slightly reeling gait with a

tendency to stagger forward and to the right. This disturbance in gait became progressively worse, so that two months later she was no longer able to walk without assistance. She soon began to complain of frequent occipital headaches which were accompanied by vomiting and pain in both eyes. She also experienced vertigo, but only when in an erect position; it would disappear as soon as she assumed a reclining position. With symptoms advancing progressively, she entered the hospital on May 2, 1932.

Examination.—There was bilateral papilledema of 3 diopters. The pupils reacted sluggishly to light. There was an unsustained nystagmus on right lateral gaze. The deep reflexes were depressed; the right abdominal reflexes were diminished. The gait was unsteady, broad based and with a tendency to fall forward and to the right; the head was tilted to the right, and the right shoulder drooped. Generalized ataxia was associated with loss of skilled movements in the right hand.

Course.—The diagnosis of a neoplasm in the vermis extending into the right lobe of the cerebellum was made. A suboccipital craniotomy was performed on her fourth day in the hospital. A smooth-walled cyst was found occupying one half of the vermis and the right cerebellar lobe in its caudal part. The cyst contained yellow gelatinous fluid and was about the size of a small egg. A well defined solid tumor, approximately the size of a walnut, was found in the medial wall of the cyst. The tumor was removed *in toto* when the wall of the cyst had been peeled away from the cerebellar tissue.

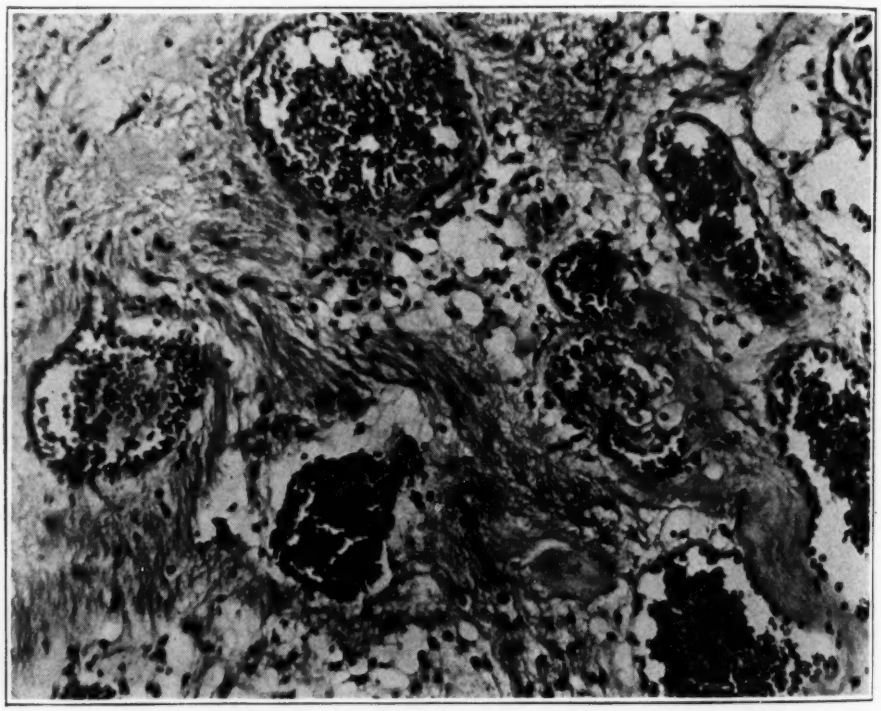

Fig. 2 (case 2).—Section exhibiting the hemangiomatous character of the tumor. Van Gieson stain; × 200.

After the operation the patient's temperature rose to 105 F. and remained elevated for ten days. During that period the child was delirious and displayed conjugate deviation of the eyes to the left and upward. Somewhat later skew deviation developed, with the right eye turned out and the left eye rotated up and out. At the end of the tenth postoperative day cerebrospinal fluid began to ooze from the wound, and with this the temperature dropped to 100 F. A bilateral Kernig sign appeared. The tissues in the line of suture became necrotic. Three days later the patient became stuporous; nuchal rigidity developed, and the temperature again rose to 105 F. The cerebrospinal fluid was found to be xanthochromic and contained 2,100 cells per cubic millimeter, 90 per cent of which were polymorphonuclear leukocytes. No organisms were isolated. The patient's condition declined, and she died twenty days after the operation.

Pathologic Examination of the Surgical Specimen.—Of significance are the great number of blood vessels which were neoplastic in character, at times assuming the character of a cavernoma, and the areas in which a reticulum was formed by the clear, often spongy (foam) cells. In addition, there were bundles of fibers running in an interlacing manner or in whorls.

Necropsy of the Brain.—Gross Examination: On removal of the occipital bone the posterior aspect of the right lobe of the cerebellum and the vermis was exposed, a circumscribed defect being exhibited. The edges of the surrounding fascia and dura were found intimately adherent to the cerebellar lobes. Both cerebellar lobes were covered by a thick purulent exudate; the right cerebellar lobe was collapsed. There was pronounced bilateral symmetric internal hydrocephalus anterior to the aqueduct of Sylvius. While the aqueduct appeared to be of normal dimensions in the anterior portion, its posterior part, near its communication with the fourth ventricle, was disorganized. The entire quadrigeminate plate seemed to be foreshortened anteroposteriorly. The fourth ventricle was noticeably widened. The overlying cerebellar hemispheres showed defects, the sites of the removed tumor. These defects within the cerebellum showed an irregular eroded surface, which was covered by a grayish exudate. The tentorium overlying the cerebellum contained a tumor nodule measuring about 2 cm. in diameter. At the base of the brain, overlying the pons and the adjacent portion of the cerebellum as well as the ventral surface of the medulla, the meninges were thickened, giving the appearance of a chronic meningitis.

Microscopic Examination: Sections of brain tissue in the proximity of the tumor showed a well defined inflammatory process. Remnants of the cystic tumor revealed a histologic structure (fig. 2) not unlike that seen in case 1. Vessels varying in size from small capillaries to large sinusoids predominated. Foam cells and collagenous fibers were also noted in fair numbers. There was also a moderate secondary gliosis.

Comment.—Little need be said about the histologic characteristics of this tumor, since it is so strikingly similar to that described in case 1. It thus can be reiterated that had not the infection set in the postoperative events would probably have been satisfactory and the subsequent clinical course might have paralleled that of case 1.

MEDULLOBLASTOMA

The term medulloblastoma was introduced by Bailey and Cushing [3] to designate a cerebellar tumor usually lodged in the fourth ventricle. They originally described it under the name of spongioblastoma, but in order to distinguish it from another type of tumor already described by Globus and Strauss [4] under the same name they adopted the now prevalent term, medulloblastoma. The name finds its explanation in the belief of Bailey and Cushing that the tumor consists of cell forms which, by virtue of their spongioblastic and neuroblastic lineage, they have designated as medulloblasts.

This tumor also is among the most common forms found in children. It is of rapid growth and is said to have a tendency to disseminate by way of the subarachnoid space. Its location, which is commonly in the midline of the cerebellum, can be detected by clinical features arising from a somewhat symmetric involvement of structures about the fourth ventricle. Bailey and Cushing summed up the syndrome associated with this type of tumor as follows:

"... the inaugural symptoms in most instances were those of increased intracranial tension, the evidence of which was likely to have been abrupt and to have been present for comparatively few months before the patient's admission to the hospital. ... [The] symptoms are headache, projectile vomiting and the rapid appearance of choked disk. ... [There may be present] a separation of the cranial sutures, which gives the characteristic cracked pot-sound to the skull on percussion. ... However, there is almost always a history of a staggering gait, and by the time of the patient's hospital admission, a full-blown

3. Bailey, P., and Cushing, M.: Medulloblastoma Cerebelli: A Common Type of Midcerebellar Glioma of Childhood, Arch. Neurol. & Psychiat. **14**:192 (Aug.) 1925.

4. Globus, J. H., and Strauss, I.: Spongioblastoma Multiforme: A Primary Malignant Form of Brain Neoplasm, Arch. Neurol. & Psychiat. **14**:139 (Aug.) 1925.

cerebellar syndrome is usually apparent. . . . In several of [the cases] there had been a history of cerebellar seizures with retraction of the head, respiratory difficulty and other symptoms which suggested a basilar meningitis."

The author also stated that dysphagia, diplopia and other signs of proximal or distal involvement of the brain may be present; that exceptions are usually encountered, and that there are cases in which the prodromal course is of longer duration.

CASE 3.—*Medulloblastoma of the fourth ventricle; craniotomy, with fatal termination and necropsy.*

History.—V. M., a white man aged 20 years, displayed a tremor of his hands for a period of four years but was otherwise well until eight months before admission to the hospital. At that time he abruptly began to complain of headaches over a period of several days. This was

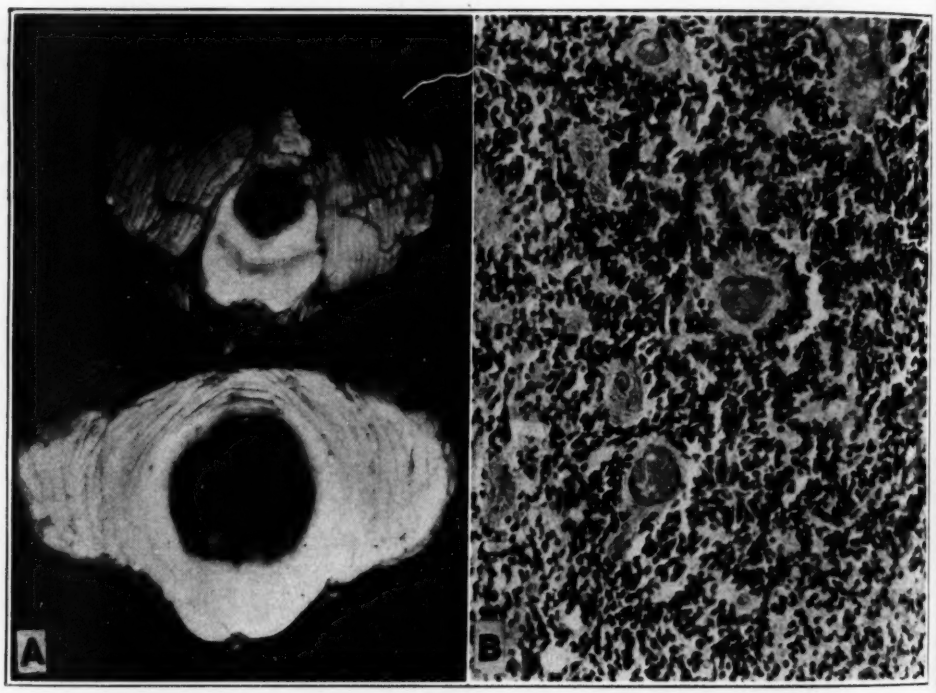

Fig. 3 (case 3).—*A*, coronal section of the cerebellum and brain stem, showing gross appearance and location of the tumor (medulloblastoma); *B*, section exhibiting the microscopic structure of and the numerous so-called pseudorosettes in the tumor. Hematoxylin-eosin stain; × 165.

followed by a period of six months during which he was apparently free of symptoms. At the end of that time there developed a gradually increasing generalized weakness and inability to stand, and a week before he entered the hospital his vision began to fail rapidly.

Examination.—There was almost complete blindness and advanced bilateral papilledema. The pupils were widely dilated and reacted sluggishly to light. A coarse nystagmus was present on lateral gaze. Generalized weakness, a broad-based gait, diminished deep reflexes, extreme cerebellar ataxia on the left side, with adiadokokinesis on that side, and dysmetria completed the clinical picture.

Course.—The diagnosis of a cerebellar neoplasm, probably midline in position, was made. This location was assumed because of the few lateralizing signs. A suboccipital craniotomy was performed (June 28, 1927), but the operation had to be abandoned before the dura had been opened, as the patient's condition became alarming. The patient died twelve hours later.

Necropsy of the Brain.—Gross Examination: A neoplasm was found invading the vermis and compressing the roof of the fourth ventricle. The pons and medulla were somewhat flattened. There was a marked symmetric internal hydrocephalus. The tumor mass measured 2.5 cm. in its transverse diameter and about 6 cm. in its long axis; it filled the fourth ventricle (fig. 3*A*) and the aqueduct of Sylvius as far as its opening in the third ventricle. It invaded the roof of the fourth ventricle and extended backward to the vermis. It was highly vascular, granular and friable and was deep brown.

Microscopic Examination: Sections of the neoplasm showed it to be cellular; the cells were small and round or oval, arranged for the most part in the form of perivascular rosette formations (fig. 3*B*). There were many thin-walled blood vessels throughout the tumor and extensive areas of recent hemorrhage. There were a few mitotic figures.

Comment.—This case was included in this study in spite of the fact that the patient at the time of admission was four years above the 16 years which we took as the upper age limit for the patients whose cases are assembled in this group. This was done because the patient was afflicted by a tremor of his hands for four years preceding the development of frank manifestations of a tumor of the brain. This tremor, in retrospect, may be regarded as having been due to early involvement of some cerebellar structure or pathway. Otherwise, the clinical picture presents no unusual features, and the clinical diagnosis was fully confirmed by the postmortem observations. The tumor is classified as a medulloblastoma mainly because of its location and gross appearance. The histologic features, though resembling those described as characterizing medulloblastoma, are not very convincing. This is particularly so in view of the fact that no neuroectodermal derivatives could be found by means of special silver and gold stains. This, as well as the vascular architecture, may well be kept in mind when a tumor in a similar location is described as a meningioma (case 25).

CASE 4.—*Medulloblastoma (?) of the vermis and the adjacent cerebellar lobes; craniotomy; gradual decline terminating in death; necropsy.*

History.—E. P., a boy aged 2½ years, three and one-half months before admission to the hospital manifested what was called "wryneck" as his head turned to the left. It persisted for about two weeks. About one month later his gait became swaying, and he often fell while making a turn. In another seven weeks he began to display inactivity and became drowsy. At about that time his left eye turned inward. Shortly before he entered the hospital, it was noted that he had a low grade papilledema and that he would retract his head when assuming a sitting position.

Examination.—The child was irritable; there were moderate bilateral papilledema and weakness of the left external rectus muscle. Both upper extremities were spastic and displayed a coarse tremor. The deep reflexes of the lower extremities were increased, more so on the left side. There were nuchal rigidity with retraction of the head and a bilateral Brudzinsky sign.

Laboratory Data.—A lumbar puncture yielded clear cerebrospinal fluid under an initial pressure of 190 mm. of water. Roentgen examination of the skull showed widening of the coronal suture.

Course.—A ventriculogram (Jan. 27, 1931) revealed an enormous internal hydrocephalus of the ventricles rostrad to the aqueduct of Sylvius. Injection of indigo carmine into the left lateral ventricle followed by lumbar puncture thirty minutes later failed to reveal the dye in the drained cerebrospinal fluid. The child's condition declined, exhibiting evidence of progressively increasing intracranial pressure. He died on the eighty-first day in the hospital.

Necropsy of the Brain.—Gross Examination: The brain was voluminous and ballooned out, with the gyri flattened. On sectioning, a large tumor was found overlying the fourth ventricle (fig. 4), involving the vermis and extending to the cerebellar hemispheres. The tumor was fleshy, hard and lobulated, with a tendency toward central softening. The aqueduct of Sylvius was compressed. The fourth ventricle was moderately enlarged, very likely as a result of traction exerted by the posterior part of the inferior portion of the tumor.

Microscopic Examination: Section showed a fairly cellular and moderately vascular tumor. While the architecture varied, a striking pattern became apparent in several areas. This

consisted in masses of loosely scattered cells surrounded by a stroma of fibrous tissue. In some parts the arrangement and character of the cells suggested the pattern of a pinealoma (fig. 5). The predominating cell was round or oval, containing a deeply staining nucleus surrounded

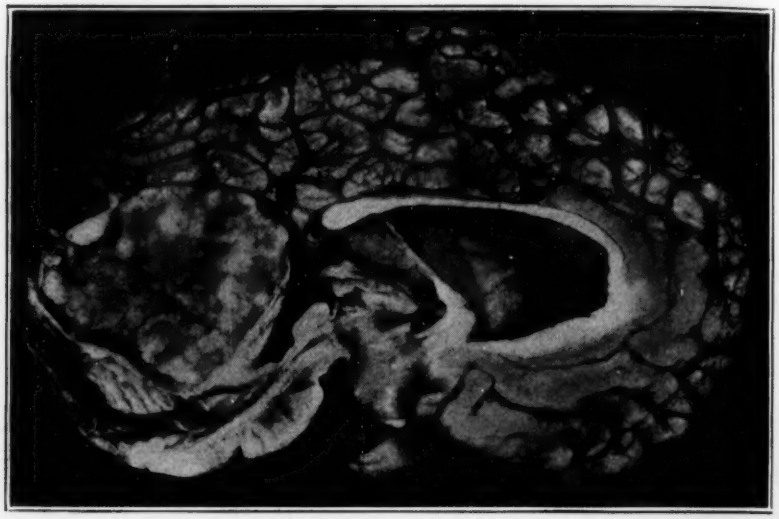

Fig. 4 (case 4).—Sagittal section of the brain, showing location and gross appearance of the tumor (medulloblastoma).

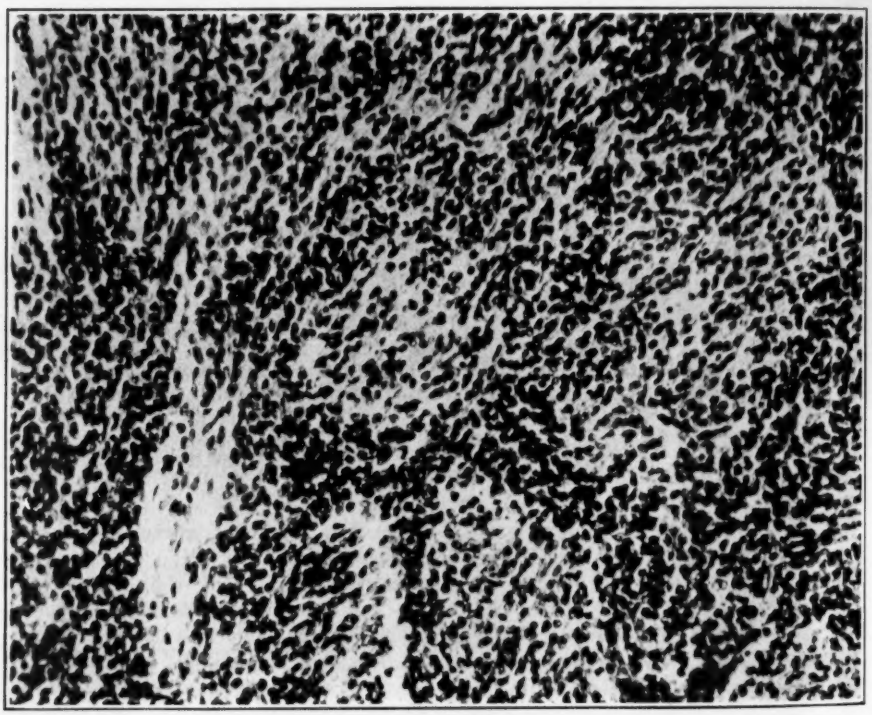

Fig. 5 (case 4).—Histologic appearance of the tumor shown in figure 4. Hematoxylin-eosin stain; × 200.

by very little cytoplasm. There were numerous mitotic figures in this group. The stroma consisted mainly of fibroblasts. In one area a band of small round cells was seen merging gradually into a band of fibrous tissue.

Comment.—The location of the tumor made the diagnosis of medulloblastoma almost mandatory. However, it is almost impossible to disregard completely the architectural design exhibited in some areas, which closely simulated that of pinealoma. Thus it would seem that tumors in and about the fourth ventricle demand a critical study before the diagnosis of medulloblastoma is accepted as final.

CASE 5.—*Medulloblastoma (?) of the vermis, extending laterally into the cerebellar hemispheres; craniotomy; rapid decline terminating in death; necropsy.*

History.—M. L., a 4 year old boy who was apparently developing normally, became subject to severe occipital headache and repeated vomiting five months before admission to the hospital. He also complained of some abdominal pain. Somewhat later he began to display some

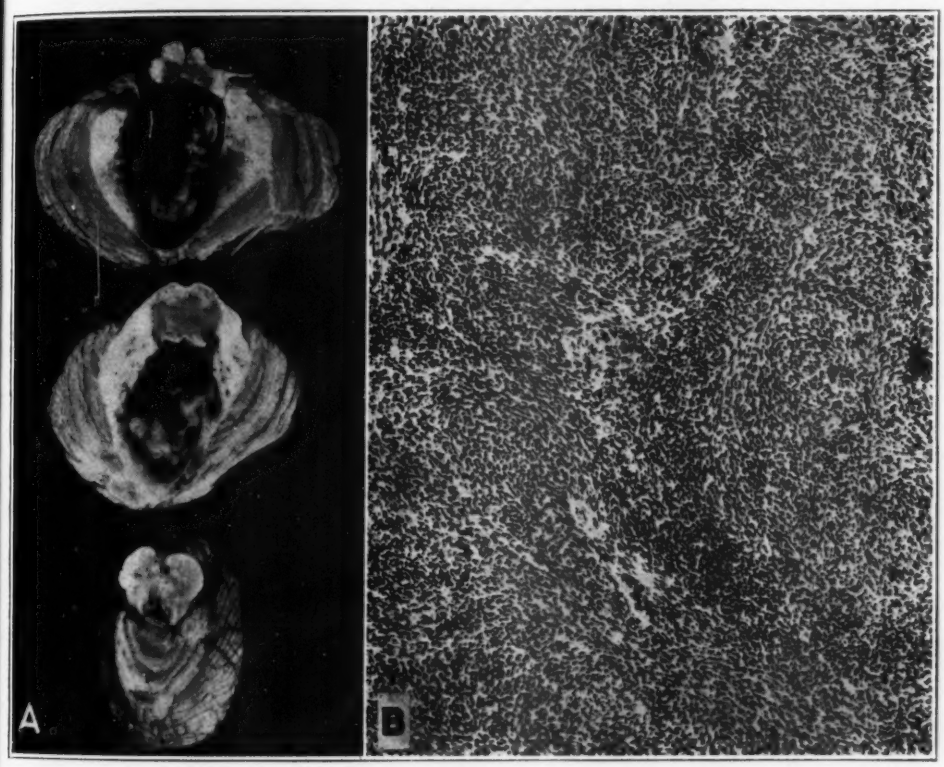

Fig. 6 (case 5).—*A*, coronal sections of the cerebellum and the related brain stem, showing the appearance and location of the tumor (medulloblastoma); *B*, section of the tumor, displaying a lobulated appearance not unlike that seen in pinealoma. Hematoxylin-eosin stain; × 88.

clumsiness in his movements, became restless and began to have nocturia (one or two urinations a night). Shortly before he was brought to the hospital (Sept. 22, 1937) all his symptoms became intensified, his gait became staggering and his eyes became crossed.

Examination.—The child had a large head. The gait was wide based and ataxic, and he had a tendency to fall, more so to the right, with the head being tilted to the left. There were bilateral papilledema, convergent strabismus and diminished corneal reflexes bilaterally. There was weakness of the left side of the face; the right side of the palate was paretic, and the voice was nasal. Ataxia, clumsiness in skilled acts and impaired check reflexes were present in both upper extremities. The deep reflexes were equal on the two sides and were diminished in the upper and active in the lower extremities. Roentgen examination of the skull showed separation of the coronal and sagittal sutures. The caloric responses were impaired on the left side.

Course.—A cerebellar tumor was diagnosed, and a suboccipital craniotomy with partial removal of a tumor of the vermis was done on September 27. The patient died shortly after the operation.

Necropsy of the Brain.—Gross Examination: There was a pronounced bilateral internal hydrocephalus, affecting the entire ventricular system. There was a pressure cone involving the left cerebellar tonsil. It bordered on a freshly made operative cavity, about the size of a golf ball, in the vermis of the cerebellum extending laterally into the cerebellar hemispheres (fig. 6*A*). A ribbon of tumor tissue was found attached partly to the walls and roof of the fourth ventricle. The tumor itself was fleshy and solid.

Microscopic Examination: The tumor consisted of densely cellular tissue; only the nuclei were visible and appeared to be arranged in rounded masses, enveloped by streams of still more intensely stained nuclei (fig. 6*B*). There were comparatively little stroma and but few blood vessels. Mitoses were not observed. In sections stained by the Bielschowsky method some cells seemed to resemble neuroblasts.

Comment.—Here also the lobulated appearance of the microscopic structure of the tumor suggested the architecture of pinealoma. The presence of a few neuroblasts, however, was a deciding factor in the ultimate designation of the tumor. Its location and gross appearance justified its grouping with the medulloblastomas.

The clinical manifestations do not call for any special comment, for the neurologic signs point definitely to the cerebellar location of the tumor. One symptom merits mention: It is the abdominal pain, which occasionally is encountered with tumor of the brain and has led to an error in diagnosis in 1 case in our general group (case 12).

To return once more to the histologic features of this type of tumor, they were described by Bailey and Cushing somewhat as follows: The typical cells contain round or slightly oval nuclei, rich in chromatin. Their cytoplasm is scanty; it either surrounds the nucleus in a ring or streams away from one pole as an indefinite tail. The cells may take a pseudo-adenomatous arrangement or form pseudo-rosettes, or aline themselves in long rows. No nerve fibers, neuroglia, or connective tissue is seen between the nuclei. Spongioblasts and neuroblasts may be found scattered among these cells.

PINEALOMA

This tumor is essentially a blastomatous growth which develops within the region of the pineal body, or, more correctly, within the quadrigeminal plate, from displaced embryonal rests. During recent years it has become less of a challenge to neurologists and neuropathologists alike. A great step forward was the recognition that pinealoma has a tendency to duplicate one or another of the several transitional stages in the developmental life of the pineal body. Globus and Silbert[5] were able to demonstrate this in their study of the embryology of this organ in the cat and in the human being by comparing several variants of pinealoma with several crucial stages in the development of the pineal body. Thus it became possible to assemble into one group a number of apparently structurally divergent types of neoplasm occurring in the same location.

The characteristic structural pattern of pinealoma is well illustrated by the first case in this group (fig. 8). There is the striking mosaic, with streams of small deeply staining cells enveloping nests of larger cells forming lighter areas. Cells of the second type, because of their size, vesicular nucleus and large margin of clear cytoplasm, correspond to the parenchyma cells of the mature pineal body. Departures from this typical organization are many, but careful study of a tumor will disclose some part of the neoplasm in which the histologic design may be

5. Globus, J. H., and Silbert, S.: Pinealomas, Arch. Neurol. & Psychiat. **25**:937 (May) 1931.

discovered. Some of the growths acquire a character indicating a low stage of differentiation and thus have been classified by Horrax and Bailey [6] as spongioblastic pinealoma.

Clinically, pinealoma presents certain features which aid in the identification of its character and location. Of these, Argyll Robertson pupils or some modification of this phenomenon, extrinsic palsies of ocular muscles, particularly of muscles supplied by the oculomotor nerves, paralysis of upward gaze, impairment of convergence, bilateral deafness, due to involvement of the posterior quadrigeminal bodies, and signs of involvement of the cerebellum, pyramidal tract and hypothalamus are usually present. Those due to involvement of the hypothalamus are in the nature of a precocious development of secondary sex characteristics.

Fig. 7 (case 6).—Base of the brain, displaying the midbrain in cross section. The tectum of the midbrain is replaced by a pinealoma.

All these symptoms, including those of increased intracranial tension, are due to the direct pressure of the tumor on the quadrigeminal plate or to the direct influence on adjacent structures and more remote parts of the brain through the development of hydrocephalus.

CASE 6.—*Pinealoma, typical in location and structure; signs and symptoms pointing to a lesion of the quadrigeminal plate; exploratory craniotomy interrupted by bleeding; progressive decline; death; necropsy.*

History.—H. F., a boy aged 13 years, had had the usual diseases of childhood but otherwise was well until 10 years of age. At that time he began to complain of headaches, which continued intermittently throughout the following three years. During the last year the headaches were associated with dizziness.

6. Horrax, G., and Bailey, P.: Tumors of the Pineal Body, Arch. Neurol. & Psychiat. 13:423 (April) 1925.

Examination.—The patient was underdeveloped. The pupils were unequal, the right being larger than the left, and did not react to light but reacted in accommodation. There was bilateral papilledema of 3 diopters. The deep reflexes were hyperactive and equal; the superficial reflexes were normal. The Wassermann reactions of the blood and of the cerebrospinal fluid were negative.

Course.—In spite of the negative serologic reactions, but because of the Argyll Robertson pupils, the patient was first regarded as suffering from juvenile dementia paralytica of tabetic type, and antisyphilitic treatment was given. The presence of papilledema, however, led to a

Fig. 8 (case 6).—Section of the tumor shown in figure 7, exhibiting the typical picture of pinealoma, with nests of large cells enveloped by streams of dark-staining small cells. Hematoxylin-eosin stain; × 163.

strong suspicion of an intracranial neoplasm. The patient was allowed to go home, but he was readmitted two months later complaining of intensified headache and vomiting.

Reexamination.—The pupils were fixed to light but reacted normally in accommodation. There was bilateral weakness of the external rectus muscles, more on the right than on the left side. There was also a slight weakness of the internal rectus muscles. There were generalized hyperreflexia with bilateral ankle clonus, a suggestive Babinski sign on the left side, slight ataxia in the right upper extremity and a cerebellar gait and posture with a tendency to fall to the right.

Subsequent Course.—At the time of reexamination a neoplasm in the region of the quadrigeminal plate was diagnosed. To verify the diagnosis a ventriculographic examination was performed, and bilateral internal hydrocephalus was revealed. It was noted also that the posterior part of the third ventricle could not be detected, which indicated an extension of the tumor into this region. An exploratory craniotomy was performed, but it was not completed because of active bleeding and a rapid decline in the condition of the patient. He died three weeks later.

Necropsy of the Brain.—Gross Examination: The surface of the brain showed evidence of a marked increase in intracranial pressure. At the base of the brain the tuber cinereum was found to be considerably distended and thinned out. Separation of the cerebral hemispheres brought into view a large mass, measuring about 2.5 cm. in its long diameter, and protruding above the dorsal surface of the cerebellum. It was found infiltrating the quadrigeminal plate (fig. 7) anteriorly and the anterior border of the cerebellum posteriorly. It extended into the cerebellar hemispheres and the right side of the midbrain. The pineal body could not be found.

Microscopic Examination: This tumor presented a strikingly characteristic cellular organization (fig. 8), with streams of small, deeply stained cells encircling nests of larger, lightly staining cells. The latter, because of their size, the vesicular character of their nuclei and the larger rims of clear cytoplasm, presented a distinct type of cell bearing a strong resemblance to the parenchyma cells of the mature pineal body.

Comment.—The arrangement of these two forms of cells, small and large, and, respectively, dark and light, gave the tumor a mosaic cell pattern such as is revealed in a survey of the various histologic pictures presented by the pineal body in its postnatal evolution. This architecture was a close imitation of patterns seen in the pineal bodies of infants from 3 to 8 weeks of age. Moreover, it invites the assumption that this tumor in its histologic makeup recapitulates one or more chapters in the histogenesis of the pineal body and suggests the strong probability that the neoplasm takes its origin from embryonal rests. While the grouping of cells thus far described forms the dominant histologic picture noted in the larger part of the tumor, there are also fields which show deviations from the typical cellular organization. In such areas, while the large cells seem to retain their outline and number, the small cells show a marked reduction in number, being apparently replaced by fibroblasts and collagenous fibers. It is not improbable that the collagenous fibers develop at the expense of the small round cells, as young fibroblasts can often be seen to develop among the gradually disappearing small dark cells. It is further demonstrated in silver preparations that wherever the small cells occur in large numbers there are few fibers but that as these cells begin to disappear fine fibers come into view in large numbers. Giant cells are not uncommon in some parts of the tumor. They are usually more often found in the vicinity of the calcified plaques. They have the appearance of foreign body giant cells and occasionally contain enclosures.

CASE 7.—*Pinealoma in the character of an embryonal rest, causing atresia of the aqueduct of Sylvius and giving rise to internal hydrocephalus and accompanying signs of increased intracranial tension; craniotomy with fatal issue; necropsy.*

History.—J. L., a boy aged 16 years, was said to have struck his head against a wooden post four months before admission to the hospital. About ten weeks later he began to complain of bitemporal headache. It was then noticed that he was becoming progressively less active and would retire earlier than was his custom. A week later he suddenly began to vomit and his headaches became more severe; the vomiting recurred more frequently. Impairment of vision set in. A month later he noticed that the left eye turned inward. In the course of time he became pallid, lost weight and continued to vomit; his headaches became more intense; weakness of both legs developed, and his speech became slurred.

Examination.—There was biparietal tenderness of the skull. The pulse rate was slow, 60 per minute. There was bilateral papilledema, more pronounced on the right. The pupils were almost fixed to light but were active during accommodation. There were bilateral weakness of external rectus muscles, poor convergence, bilateral ptosis of the eyelids and slight weakness

of the right side of the face. The patient's gait was somewhat unsteady; the right arm did not swing normally, and the right shoulder was somewhat elevated. Slight nuchal rigidity was accompanied by a bilateral Kernig sign. The right lower extremity was weak; the fingers of the right hand displayed moderate pseudoathetoid movements. The deep reflexes were depressed. The abdominal reflexes were easily exhaustible on the right; they were absent on the left.

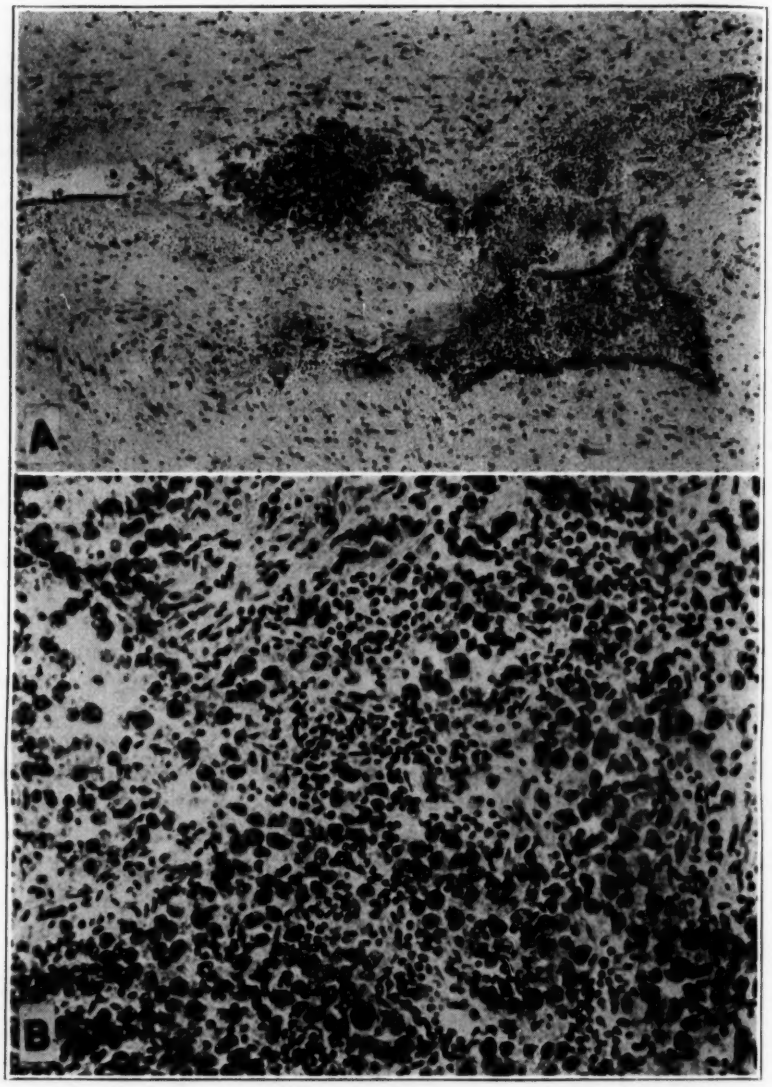

Fig. 9 (case 7).—*A*, section of the midbrain in the region of the aqueduct of Sylvius, showing the latter to be almost completely obliterated. Slightly dorsolateral to the aqueduct is a small nest of tumor cells. Hematoxylin-eosin stain; × 44. *B*, the cell types and organization characteristic of pinealoma in the small tumor nodule shown in *A*. Hematoxylin-eosin stain; × 230.

Laboratory Data.—A lumbar puncture yielded clear cerebrospinal fluid under an initial pressure of 300 mm. of water. It contained 22 lymphocytes; a Pandy test gave a reaction of 4 plus. Roentgen examination of the skull showed a group of irregular calcifications in the middle of the skull, below the usual position of the pineal body. The coronal sutures were widened, and the posterior clinoid processes were somewhat decalcified.

Course.—A ventriculogram (May 19, 1937) showed dilatation of the third and lateral ventricles. It was thought that the aforementioned calcium deposits were within a tumor mass which was thought to be protruding into the posterior wall of the third ventricle. A craniotomy was performed (May 20); a brownish tumor in the region of the pineal body was found, and part of it was enucleated. The patient died fourteen hours later.

Necropsy of the Brain.—Gross Examination: There was considerable disorganization of tissue in the dorsal part of the midbrain and pons, the site of the operative intervention. There were marked internal hydrocephalus affecting the lateral and third ventricles; severe disorganization of structures about the posterior part of the third ventricle and the posterior part of the left lateral ventricle; some discoloration of the ependymal lining and pronounced swelling and disorganization of the choroid plexus; disorganization of the entire left occipital lobe, and dislodgment and disorganization of the aqueduct of Sylvius.

Microscopic Examination: Sections of the midbrain in the region of the aqueduct of Sylvius revealed tumor tissue with severe hemorrhage. The aqueduct (fig. 9*A*) was partially obliterated by a small mass of tumor tissue, and in its remaining part it was filled with desquamated ependyma, blood cells and macrophages. The tumor mass was cellular and displayed a structural design much like that seen in the typical pinealoma (fig. 9*B*) or in the normal pineal body during its early postnatal development. The two types of cells were readily distinguishable, one having a large pale-staining vesicular nucleus and the other, a smaller cell, containing a small dark-staining nucleus. The former maintained a nestlike arrangement and were surrounded by somewhat irregular streams of cells of the latter type.

Comment.—This case strongly suggests the probability that a displaced embryonal rest was the cause of the neoplastic lesion which obstructed the aqueduct. This, in turn, caused internal hydrocephalus and the accompanying clinical manifestations. The anatomic observations in this case are in remarkable accord with the view expressed as to the probable blastomatous character and heterotopic origin of pinealomas in general.

CASE 8.—*Pinealoma containing a large colloidal cyst and a small mass of neoplastic tissue, the latter resembling in structure a well differentiated pineal body, completely replacing the tectum mesencephali and invading the left lateral ventricle; diagnosed as a paraqueductal tumor; tumor not disclosed by exploratory suboccipital craniotomy; fatal issue; necropsy.*

History.—A. G., a girl aged 11 years, had been apparently well until two years before examination, when she fell down a flight of stairs and landed on her head. Her recent illness dated back to four months before admission to the hospital, when she complained of abdominal pain, nausea and occasional vomiting. Her condition remained unchanged until two months before admission, when she began to complain of headache. For five weeks before admission she had diplopia and impairment of vision.

Examination.—The patient was drowsy but could easily be aroused. She was resistant to examination and irritable. She yawned frequently. There was bilateral papilledema, with an elevation of about 2 diopters. Her pupils were equal and reacted sluggishly to light (reaction in accommodation was not recorded). The right eyelid drooped, and there was conjugate deviation to the right. The deep reflexes were depressed. The gait was unsteady, with a tendency to fall to the right. There was a cerebellar posture of the head, with the chin carried to the right and the occiput to the left. The cerebrospinal fluid was reported as normal, and the Wassermann reaction of the blood was negative.

Course.—A diagnosis of neoplasm near the aqueduct of Sylvius was made. A suboccipital craniotomy did not disclose the tumor. The patient's vision declined rapidly, and she became totally blind, with the pupils having become fixed to light. She also became entirely deaf. Six weeks after admission, the right upper and lower extremities were completely paralyzed and showed resistance to passive movement, but no contractures were present. There was a curious posture of the left hand, the wrist being flexed while the fingers were slightly extended. There was a slow, rhythmic, coarse tremor of the left hand. The patient deteriorated slowly and died ten weeks after admission.

Necropsy of the Brain.—Gross Examination: The brain was noticeably flattened. When the occipital lobes were raised, a soft tumor was exposed. It extended from the superior vermis to the quadrigeminal plate and beyond it. A large colloid cyst was found occupying the right lateral ventricle (fig. 10*A*). It completely filled this ventricle as far forward as the foramen of Monro and posteriorly as far as the junction of the descending and posterior

horns. It then extended backward over the roof of the aqueduct of Sylvius, where it was embedded in the depression over the vermis and the lateral lobe of the cerebellum. In its posterior extent it almost completely destroyed the tectum of the midbrain and some of the tegmentum on the left side. The ventricular cavities were greatly distended. The third ventricle was widely open but was displaced to the left and deformed. The cyst had a well defined capsule, which measured about 2 mm. in thickness. It was free in its anterolateral aspect but adherent to adjacent tissue on its ventromedian aspect. It was filled with a jelly-like

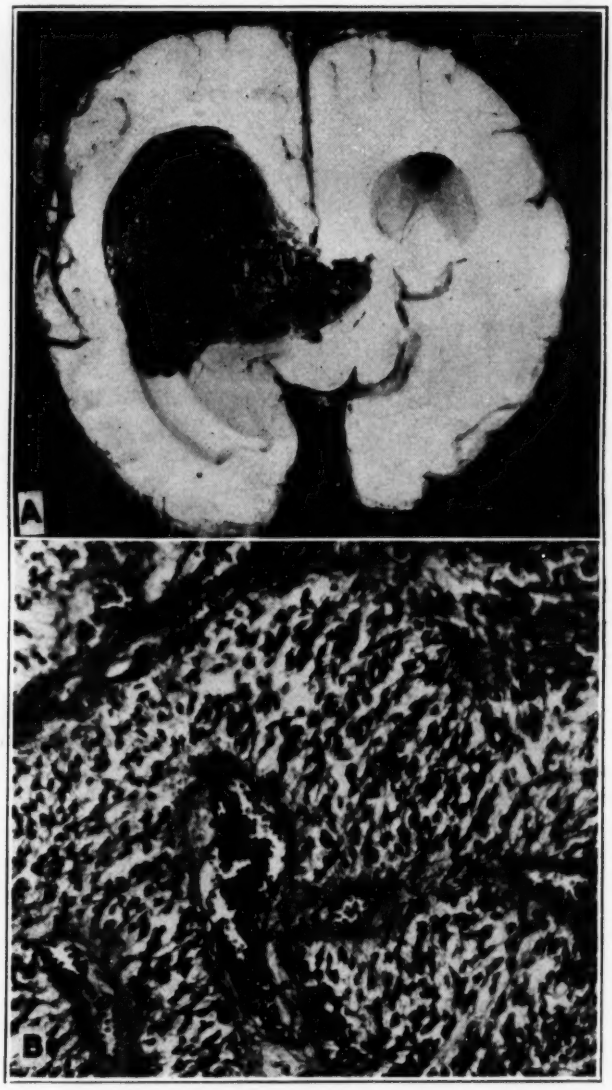

Fig. 10 (case 8).—*A,* coronal section of the brain, showing a large tumor mass extending from the roof of the midbrain and breaking into and filling up the left lateral ventricle; *B,* section of the tumor, displaying the histologic structure, which closely simulates that of the mature pineal body. Hematoxylin-eosin stain; × 125.

substance of a grayish green hue; on its ventral surface it presented a small spongy mass, cystic in some parts. These areas bore a striking resemblance in structure to the pineal body. The pineal body could not be found.

Microscopic Examination: The structure of this tumor (fig. 10 *B*) had a strong similarity to that of the adult pineal gland. There were the lobulation, with rather prominent interlobular

trabeculae, typical of the adult pineal body and the reticulum-like formation resulting from the interlacement of the short processes arising from the cells, which contained little cytoplasm but had rather large irregularly outlined nuclei.

Comment.—The diagnosis of paraqueductal tumor in this case was made because of the combination of signs pointing to involvement of the midbrain (fixation of pupils and total bilateral deafness) and the cerebellum. Particularly significant were the fixation of the pupils and the loss of hearing. Histologically the tumor suggests the diagnosis of hyperplasia of the pineal gland, but because of the youth of the patient and the size of the tumor the neoplastic character is the more likely. The pinealoma was of the highly differentiated makeup that may be classed as an adult pinealoma.

CASE 9.—*Pinealoma of spongioblastic variety, which seemed to yield to high voltage roentgen therapy, but only temporarily; surgical intervention considered to be too hazardous; fatal termination without operation; necropsy.*

History.—H. V., a 16 year old school girl, was admitted to the hospital on April 27, 1939, complaining of headaches of ten weeks' duration, intermittent vomiting and ringing noises with auditory hallucinations for four weeks. Shortly thereafter she became progressively weaker and took to bed. She became somnolent and could not sit up in bed without experiencing vertigo. It became difficult for her to initiate urination.

Examination.—The patient was drowsy and yawned frequently; her pulse rate was slow, 56 per minute. The optic disks were hyperemic; the pupillary reactions to light were paradoxic; upward gaze was paralyzed, and downward gaze was weak. There were intermittent convergence spasms, bilateral weakness of the external rectus muscles and diplopia. Hearing was impaired bilaterally, and its cause was regarded as central in origin. There was slight dysdiadokokinesis on the left side. The deep reflexes were more active on the left side, and Babinski and Chaddock signs were elicited bilaterally.

Course.—A diagnosis of an infiltrating lesion of the quadrigeminal plate was made. At first the patient was quite cooperative, but she soon became subject to transient attacks of loss of consciousness during which she would become rigid. Drowsiness increased, and advancing papilledema developed. A ventriculogram (May 11) showed symmetric dilatation of the lateral and third ventricles. In view of the poor surgical risk, craniotomy was deferred and radiation therapy was administered, which at first gave remarkably good, though only temporary, results; another decline set in. She was brought to the hospital on October 9. During the previous week stiffness of and pain in the neck on turning the head had developed; she vomited repeatedly. Tremors of the hands and feet appeared, especially during sleep, and general weakness set in.

Second Admission.—At this time there was bilateral papilledema; the pupils were dilated and fixed to light and in accommodation; there was a "refraction nystagmus" and left internal strabismus and convergence spasm during attempted accommodation. The initial pressure of the cerebrospinal fluid was 220 mm. of water; the total protein content was 50 mg. per hundred cubic centimeters. The patient again received roentgen therapy and again showed a great deal of improvement, permitting her to return home. Again, however, symptoms recurred, and she was brought back to the hospital on December 26.

Third Admission.—The patient was in semistupor and displayed occasional convulsive seizures characterized by spastic flexion of the elbows and extension of the fingers and lower extremities. There was evidence of increased intracranial pressure. The pupils at this time were contracted and were fixed. She died on Jan. 9, 1940.

Necropsy of the Brain.—Gross Examination: The pons was firm and appeared enlarged. On separation of the cerebral hemisphere (fig. 11 *A*) in the region of the splenium of the corpus callosum a hard mass infiltrating the pons was found. The pineal gland could not be found. The body of the left ventricle was smaller than the right owing to a swelling and the presence of a tumor mass in the thalamus. The third ventricle was narrow in its upper portion, above the massa intermedia, but it was widely dilated below in the region of the hypothalamus. The aqueduct of Sylvius was almost completely closed at its anterior end by tumor tissue. The left thalamus at about the level of the middle commissure showed a round, fairly well demarcated tumor occupying its dorsal two thirds and about one half of its width.

The tumor mass occupied almost the entire left thalamus and spread over to the opposite side, affecting the medial half of the right thalamus. It passed posteriorly into the midbrain, replacing completely the quadrigeminal plate, the paraqueductal area and the tegmentum. The substantia nigra was also involved on the left side and was narrowed and compressed on the right side. Farther posteriorly, the tumor tissue involved structures directly ventral to the aqueduct, sparing the red nucleus on the right but not on the left side.

Microscopic Examination: In some parts of the tumor the cellular arrangement was much like that seen in the more typical pinealoma. Aggregations of small cells bordering on areas containing large cellular elements were recognized. The latter (fig. 11 *B*), however, showed great deviations in size and form from the large cells seen in the typical pinealoma. They were frequently multinuclear and displayed a number of variations in form. Some of them were giant-like and irregular in outline; others were equally large but oval or round. In other parts of the tumor the structure was strikingly different. Here the cellular aggregations occupied narrow spaces between partitions of connective tissue. The cells here were predominantly

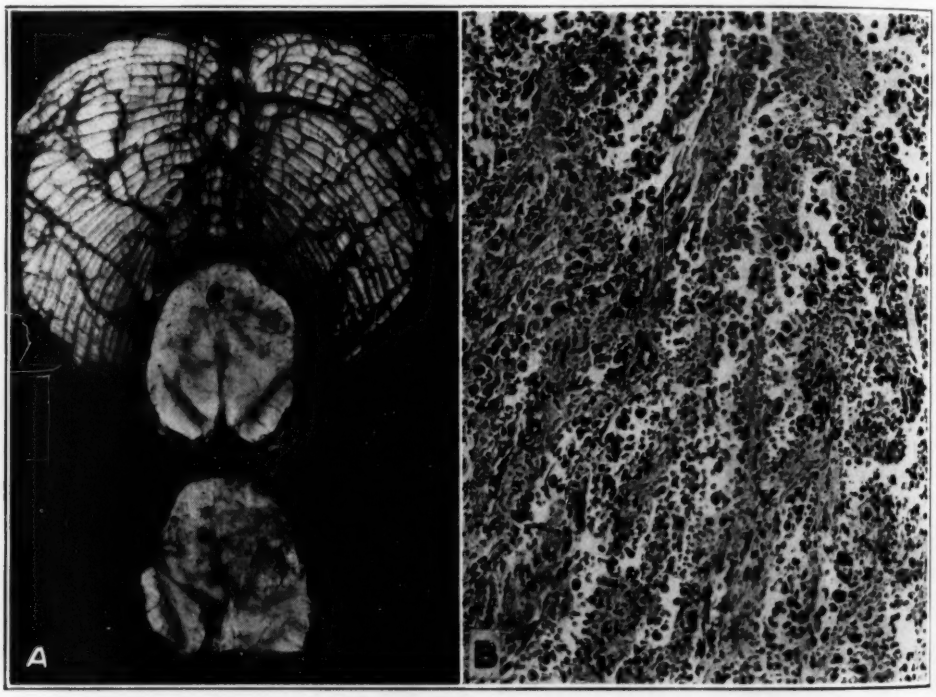

Fig. 11 (case 9).—*A*, coronal sections of the midbrain, showing the appearance and location of pinealoma; *B*, section of the tumor, displaying the histologic character, which exhibits the presence of many giant multinucleated cells such as are found in the spongioblastic variety of such tumors. Hematoxylin-eosin stain; × 80.

large, most frequently multinuclear and not unlike the type seen in the malignant form of glioma, better known as spongioblastoma multiforme.

Comment.—Clinically this case may be regarded as presenting a characteristic picture of a tumor of the quadrigeminal plate with extensions into neighboring parts of the midbrain. The paralysis of upward gaze, the intermittent convergence spasm, the paradoxic pupillary reactions, the loss of hearing and the moderate cerebellar signs point to such a localization of the lesion. The histologic character of the tumor deviates from the typical structure of pinealoma and belongs to the type described by Horrax and Bailey [6] as spongioblastic pinealoma. The malignant character of the growth is explained by this histologic departure.

CRANIOPHARYNGIOMA

It is rather puzzling to find that adenoma of the pituitary gland is a type of tumor rare among children, while, in striking contrast to this, the suprasellar or parahypophysial tumor arising from remnants of the craniopharyngeal duct is common. This type of neoplasm most often assumes the form of a cyst,[7] which may contain an intramural nodule having the characteristic cellular ingredients. The cyst is usually filled with a greenish brown viscid fluid, rich in cholesterol crystals. There are, however, some tumors of this variety which are solid and are structurally best described as adamantinoma or ameloblastoma. The latter name, as recently explained by MacCallum,[7e] is based on the similarity of the marginal cells with their palisade formation to the secreting cells of the enamel organ of the teeth.

Craniopharyngioma, because of its suprasellar location, seldom causes enlargement of the sella turcica, although it does provoke erosion of the clinoid processes. Not infrequently it extends upward to compress, dislodge, distort or invade the floor of the third ventricle and thus causes hypothalamic disturbances.

The clinical manifestations are due to the direct influence of the tumor on the neighboring structures at the base of the brain, such as the optic chiasm, the optic tracts or nerves, the oculomotor nerves, the infundibulum and the pituitary gland, and the midbrain and the structures within it.[7b]

Thus, in addition to signs of increased intracranial tension, there are visual disturbances (diplopia, amblyopia) and disorders of the vegetative functions (drowsiness, polydipsia, polyuria, dwarfism and other manifestations of dyspituitarism).

The presence of calcium deposits in the wall of such a tumor often leads to recognition of the lesion by roentgen examination.

CASE 10.—*Craniopharyngioma with the typical features of hypothalamic disorder and signs of interpeduncular involvement; exploratory craniotomy; death; necropsy.*

History.—A girl aged 6 years, who had had no previous illness and had been normal until the onset of symptoms six months before her admission to the hospital, became seriously constipated. Her sleep became disturbed, and she became restless. Her appetite became poor, and, because of constant thirst, she demanded water frequently. With the increase of thirst and the increase of water intake, there was an increase in volume and frequency of urination. Several weeks later the diagnosis of diabetes was made, and the child was treated accordingly. She was nevertheless losing strength and became easily fatigued; she gave up playing, became irritable and finally took to bed because of constant headache and general weakness. A week before her admission to the hospital it was noted that the child's mouth was drawn to one side and that her left shoulder drooped and frequently twitched.

Examination.—The patient was somewhat undersized, with a profuse growth of lanugo hairs all over the body. There were ptosis of the right eyelid and external strabimus of the right eye. The left pupil was larger than the right. Both pupils reacted to light and in accommodation. There were weakness of the left side of the face and slight weakness of the left arm and hand, the latter being held in a hemiplegic position. There was slight weakness of the left leg. The deep reflexes were more active on the left than on the right side, though generally reduced. The Babinski reflex was doubtful, but gait and station were normal. The abdominal reflexes could not be elicited. The cerebrospinal fluid was sterile. The diagnosis of a neoplasm involving the posterior lobe of the pituitary gland and the right crus cerebri was made.

Course.—The patient was subjected to an exploratory craniotomy, which terminated fatally.

7. (*a*) Erdheim, J.: Ueber Hypophysenganggeschwülste und Hirncholesteatome, Sitzungsb. d. math.-phys. Cl. d. k.-bayer. Akad. d. Wissensch. zu München **113**:537, 1904. (*b*) Ehlers, H. W. E.: Ein Beitrag zur Kenntnis des Infundibularzystems des menschlichen Gehirns, Virchows Arch. f. path. Anat. **119**:542, 1910. (*c*) Globus, J. H.: Teratoid Cyst of the Hypophysis, Arch. Neurol. & Psychiat. **9**:417 (April) 1923. (*d*) Critchley, M., and Ironside, R.: The Pituitary Adamantinoma, Brain **49**:437, 1926. (*e*) MacCallum, W. G.: Adamantinoma of the Hypophyseal Duct, J. Mt. Sinai Hosp. **8**:798, 1942.

Necropsy of the Brain.—Gross Examination: When the frontal lobes were raised, a larg purple, fluctuating mass presented itself at the base of the brain. It covered the optic chias to which it was adherent (fig. 12*A*). Posteriorly, it filled the entire interpeduncular spac Its bulging inferior and partially free surface was prolonged into a funnel-shaped proce which seemed to be continuous with the pituitary body. The latter was extremely small a compressed and was lodged in a shallow sella turcica. The base of the superior surface of t mass was firmly implanted in the substance of the brain. The optic chiasm and tracts we flattened. The tuber cinereum and the mamillary bodies could not be identified, since the flo of the third ventricle was stretched and flattened by the tumor mass, which almost obliterate the cavity of the third ventricle. The cerebral peduncles were displaced laterally and we reduced in size. This was particularly pronounced on the right side. During the process detachment of the brain from the base of the skull, the neoplasm was punctured, and a dar brown, granular, semifluid mass escaped from the cavity. When the latter was opened it wa noted to be a rather thin-walled cyst, lined by a corrugated membrane which was studded wit numerous small glistening elevations. Cholesterol crystals were demonstrated in the contents the cyst. The cyst was 4 cm. in length and about 3.5 cm. in width. The third nerve on t

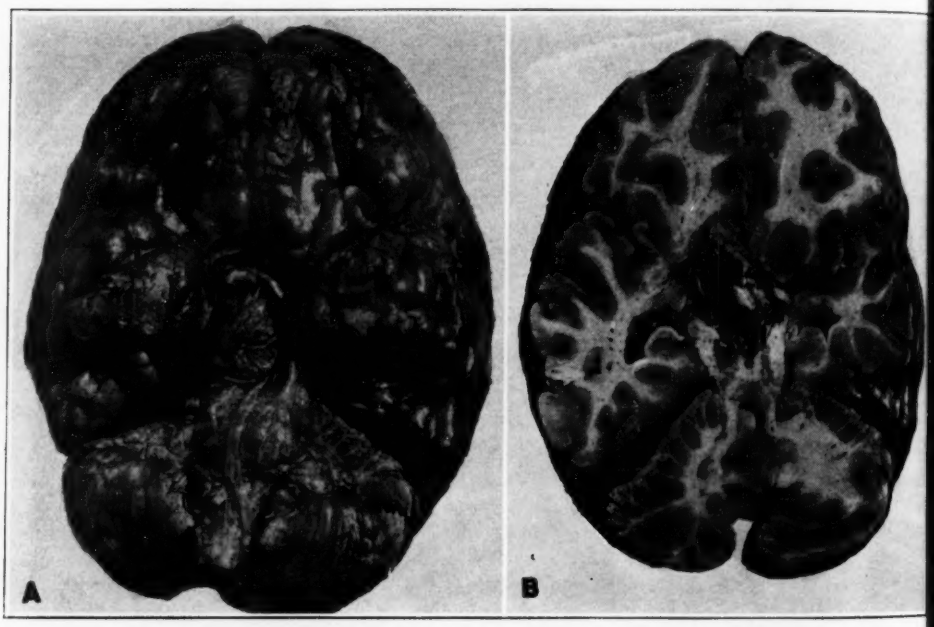

Fig. 12 (case 10).—*A*, the base of the brain, displaying a cystic tumor (craniopharyngioma) in the interpeduncular space; *B*, horizontal section of the brain, displaying the cystic character of the tumor containing a small intramural nodule.

right side was compressed and flattened by the neoplasm. A horizontal, longitudinal section of the brain gave a still better view of the gross structural changes that were brought about by the neoplasm (fig. 12*B*). The lining of the cyst was thus brought into view; it had the appearance of a mucous coat. At the left anterior portion of the cyst, the wall was thickened, giving rise to an elevation, cartilaginous in consistency.

Microscopic Examination: The wall of the cyst was lined by stratified squamous epithelium of an embryonal character. Here and there on the surface of the epithelial lining there was a heaping-up of cells which had a concentric lamellated arrangement, giving the appearance of epithelial pearls (fig. 13*A*). The latter were in various stages of degeneration, showing central areas of calcification, and were frequently surrounded by foreign body giant cells. Beneath this epithelial lining, there was a stroma of connective tissue, in which glandular tissue of both salivary and sebaceous types were found. Embryonal cartilage, dense fibrous tissue, embryonic mucous tissue and bone (fig. 13*B*), representing all the osteogenetic elements, were also present. Keratohyalin granules were demonstrated in the squamous epithelial lining, and developing hair follicles were present in the form of hair germs.

Comment.—It is evident that this tumor presented in its structure all the ements of the ectodermal and mesodermal components of the primitive skin, to hich other embryonal tissues of mesodermal origin (bone, cartilage, mucous embrane and connective tissue) were added. While it is possible that the calcified abeculae and the osteogenetic elements were the result of metaplasia in a generated area, the hair follicles and sebaceous cells could not have had this

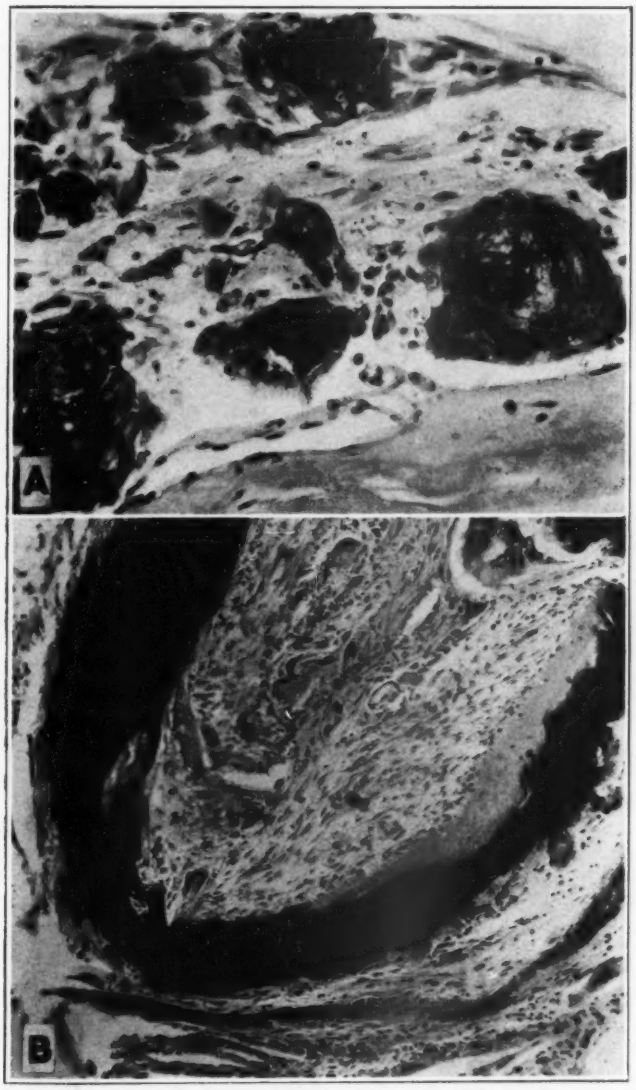

Fig. 13 (case 10).—*A,* section of the intramural nodule of the tumor shown in figure 12, exhibiting many collections of keratinized epithelium. Hematoxylin-eosin stain; × 133. *B,* section of the same tumor, exhibiting an area of calcification and many foreign body giant cells. Hematoxylin-eosin stain; × 89.

origin. We are therefore dealing here with a growth which is bigerminal and thus autochthonous.

In comparing this neoplasm with those described by Erdheim,[7a] who stated the belief that the subinvoluted craniopharyngeal duct is the site of origin of such

tumors, it is noted that there is striking similarity between this cyst and those Erdheim derived from the hypophysial duct. The only difference is that he failed to find hair follicles or keratohyalin granules in the epithelial lining, while these structures were found in the tumor here described. Erdheim laid emphasis on the keratin reaction, suggesting that the presence of this substance differentiates between tumors derived from the subinvoluted hypophysial duct and the dermoid cysts described by Bostroem. Tumors of the hypophysial duct did not show hair follicles or keratohyalin granules, while these were constantly present in the dermoids. This finer differentiation has already been disputed by Ehlers,[7b] who described a tumor similar to ours in which he was able to demonstrate keratohyalin material. Ehlers came to the conclusion that in spite of the intimate relation of the tumor to the infundibulum and the possible origin of such a tumor from the primitive oral cavity the presence of keratohyalin places this tumor with the dermoid cysts. He also suggested that the failure of Erdheim to demonstrate keratin can be accounted for by the method of fixation, as some of the tumors had been kept for many years as museum specimens.

Bailey and Bremer [8] have shown that the clinical symptoms of diabetes insipidus, such as polyuria and polydipsia, can be provoked with certainty by a lesion produced in the postinfundibular region of the hypothalamus and that the removal of the posterior lobe of the hypophysis does not lead to the permanent production of such symptoms. They concluded, therefore, that there is no evidence supporting the older views which assert that a hypophysial lesion is responsible for the symptoms of diabetes insipidus. This case and others here reported offer further support of the views expressed by the foregoing authors, for the polydipsia and polyuria are striking symptoms which appear late in the course of the disease and the anatomic findings show that the pituitary gland is usually intact, though it is commonly somewhat compressed. The hypothalamus, on the other hand, is seriously and distinctly disorganized.

CASE 11.—*Craniopharyngioma causing hypothalamic disorder and uncinate fits; craniotomy; interpeduncular cyst found and partially removed, followed by recovery; death two years later of mastoid infection; necropsy.*

History.—A boy aged 3½ years was admitted to the hospital complaining of recurrent headaches of three months' duration. The pain would start in the neck and would radiate to the forehead. Almost regularly the headaches would appear in the morning and would last four to five hours. In the meantime it was noticed that his left eye turned outward. A month before entering the hospital the patient's headaches were accompanied by vomiting. His appetite diminished, and he lost 10 pounds (4.5 Kg.) during that month. At about the same time he began to experience excessive thirst, and he urinated more frequently. About a week before entering the hospital he complained of bad odors, not detected by others present in the room.

Examination.—The patient manifested features of a hypopituitary constitution. There were a left central facial palsy with questionable left hemiparesis, a positive Babinski sign on the left and diminished abdominal reflexes on the left. The pupils were equal, round and regular and reacted to light and in accommodation; there was primary atrophy of the left optic nerve; the visual fields could not be studied because of the age of the patient.

Laboratory Data.—The results of examinations of the urine and of cytologic study and serologic tests of the blood were normal. A lumbar puncture revealed normal cerebrospinal fluid under an initial pressure of 320 mm. of water (the child was straining slightly throughout the procedure). Roentgen examination of the skull showed deformity of the sella turcica and erosion of the posterior clinoid processes. There were several small concretions in the sella and two small calcifications above it.

8. Bailey, P., and Bremer, F.: Experimental Diabetes Insipidus, Arch. Int. Med. 28: 773 (Dec.) 1921.

Course.—A suprasellar cyst was diagnosed, and the patient was operated on in two stages. A suprasellar cyst was found projecting in front of the chiasm. It was filled with fluid and some calcareous substance. The left lateral and posterior limits could not be visualized, but it was estimated that about one half to three fourths of the projecting cyst was removed. After the operation the patient's temperature rose to 106 F., but it returned to normal the next day. Convalescence and recovery were highly satisfactory, except that the atrophy of the left optic nerve became more advanced and a definite pallor of the right nerve head appeared. The excessive thirst and urination continued for a while, but a note ten months later read: "The patient no longer has diabetes insipidus." The fundi still showed atrophy of the optic nerve, and vision was poor in the left eye.

Two years later the patient returned to the hospital with otitis media, which developed in the right ear following measles. The neurologic examination revealed a questionable bilateral

Fig. 14 (case 11).—Base of the brain, exhibiting a cystic tumor (craniopharyngioma) in the interpeduncular space.

weakness of the internal rectus muscles, temporal pallor of the right optic nerve and pronounced primary atrophy of the left optic nerve, and a Babinski sign and absence of abdominal reflexes on the left. Thrombosis of the right lateral sinus developed, requiring ligation of the internal jugular vein. A mastoidectomy was also started, but the patient's condition suddenly declined, interrupting the operation. During the next seventeen hours he had four generalized convulsive seizures, terminating in death.

Necropsy of the Brain.—Gross Examination: A large cyst (fig. 14) was found occupying the entire interpeduncular space and extending forward toward the cerebral hemispheres and underneath them. Both optic nerves were displaced and compressed by the cyst. The cyst mass was thin walled and contained greenish yellow material and pockets of gelatinous substance. It was adherent to the sella turcica, which was exceedingly deep, about 1.5 cm. in depth.

Microscopic Examination: The wall of the cyst was lined by primitive stratified epithelium (fig. 15 *A*), which in places acquired the stratified character with the surface cells undergoing hornification and desquamation (fig. 15 *B*).

Comment.—This case again illustrates the occurrence of signs of diabetes insipidus with a lesion in the floor of the third ventricle. More significant is the fact that the signs of diabetes insipidus disappeared after the tumor was partially

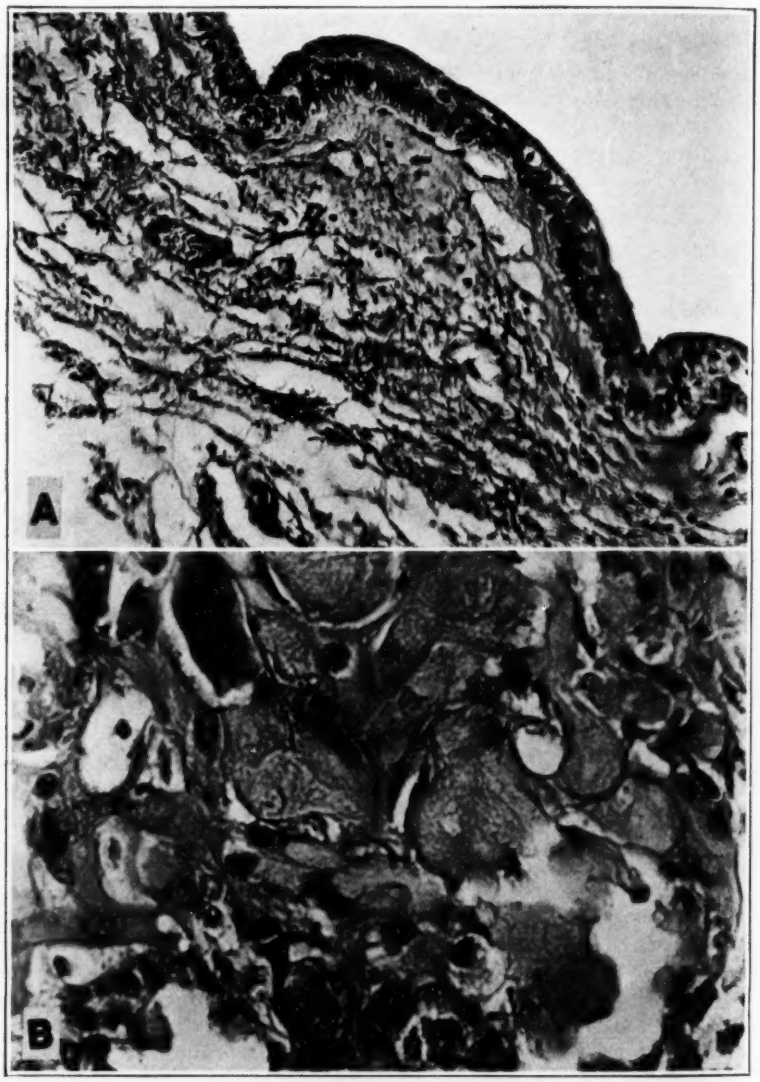

Fig. 15 (case 11).—*A*, section of the cystic tumor, showing primitive epidermis lining the cyst. Hematoxylin-eosin stain; × 194. *B*, section of the same tumor displaying a number of hyalinized epithelial cells.

opened and pressure on the floor of the third ventricle released. Highly important is the fact that with only partial removal of the tumor the patient was apparently well for a period of two years; and had it not been for the aural infection it is possible that the patient would have continued to do well for some time. It would seem that the less radical step is the procedure of choice in a case of craniopharyngeal cyst.

CASE 12.—*Craniopharyngioma giving rise to manifestations of a hypothalamic disorder and with the histologic structure of an adamantinoma.*

History.—A boy 10½ years of age was seen only once in the outpatient department of the hospital. He was unusually obese, with excessive fat about the hips, breasts and genitalia. The formation of the scrotum suggested that of a vulva. He gave the impression of having Froehlich's syndrome. He was not seen again until he was brought to the hospital with a history of acute illness and signs of appendicitis. An inflamed appendix was removed. Soon after operation he began to complain of headache and a rigid neck developed.

Examination.—There was advanced bilateral papilledema with retinal hemorrhages. The blood pressure was 150 systolic and 115 diastolic. The patient was drowsy and at times stuporous. Roentgen examination of the skull was unsatisfactory.

Fig. 16 (case 12).—The base of the brain, showing a tumor (adamantinoma) in the interpeduncular space.

Course.—The Froehlich syndrome coupled with the papilledema, headache and advancing drowsiness suggested the diagnosis of a cerebral neoplasm, probably suprasellar. At operation a cyst was found and was excised. The patient remained in good condition for several hours, but eight hours later his temperature rose abruptly to 105 F.; it then dropped to 103.4 F. but rose again just preceding death, which occurred seventy hours after operation.

Necropsy of the Brain.—Gross Examination: The remains of the cyst were seen in the interpeduncular space (fig. 16). There was no gross surgical damage to the brain which could account for the elevation of temperature or the rapid fatal termination. The cerebral convolutions were flattened; the olfactory bulbs were slightly distorted and traumatized. The optic nerves and chiasm were edematous. Below and behind the optic chiasm was a small tumor mass. The posterior clinoid processes and the dorsum sellae were eroded and thinned.

The venous and air sinuses and the middle ears were normal. The lateral ventricles were symmetrically dilated. The third ventricle was somewhat larger anteriorly. In front of the middle commissure all that was left of the tumor was a segment of its wall situated directly inferior to the anterior portion of the floor of the third ventricle. It was adherent to the optic chiasm, which was somewhat flattened. The oculomotor nerves were displaced posteriorly and laterally. The pituitary body was found attached to the tumor.

Fig. 17 (case 12).—*A*, histologic (adamantinomatous) structure of the tumor. Hematoxylin-eosin stain; × 12. *B*, section of the tumor, displaying areas of calcification and free cholesterol crystal spaces. Hematoxylin-eosin stain; × 78.

Microscopic Examination: The histologic features of this tumor included the presence of areas suggesting the structure of adamantinoma (fig. 17 *A*) and other areas in which spaces corresponding to cholesterol crystals (fig. 17 *B*) were washed out by solvents.

Comment.—The abnormal obesity of the patient and the poor development of the secondary sex characters are common conditions accompanying tumors involving the floor of the third ventricle. It is also probable that the hypertension

present at this age in a boy who displayed other vegetative dysfunctions could also have been traced to a lesion in this location. The sudden rise in temperature may be explained by the dislocation of the floor of the third ventricle as the result of the sudden collapse of a cystic pocket in the tumor. These views are strengthened by the fact that the pituitary body was found to be normal. Of interest also are the abdominal symptoms (probably cerebral in origin) which led to the appendectomy.

INFUNDIBULOMA

A form of tumor arising from the infundibulum was recently described by one of us (J. H. G.)[9] and, accordingly, was named by him infundibuloma. It is neurohypophysial in derivation and simulates the structure of the infundibulum, including the posterior lobe of the hypophysis, by a characteristic vascular pattern which is common to both the tumor and the infundibular region. Clinically, it resembles other tumors in the interpeduncular or suprasellar region and for the present does not disclose any special features.

CASE 13.—*Interpeduncular tumor, originating in the floor of the third ventricle, identified as an infundibuloma; main clinical features referable to vision; pulse and temperature discord; craniotomy; death; necropsy.*

History.—A school boy aged 13½ years was said to have been well until the age of 11 years, when he began to have mild frontal headaches which occurred once a week. During the next two years there were apparently no other symptoms; then he began to complain of impairment of vision, which progressed so rapidly that by the end of one week he found reading to be very difficult. Within another few weeks he became subject to occasional transient diplopia, with the images appearing on the same horizontal plane. Shortly thereafter severe headaches became more frequent, occurring almost daily and lasting several hours at a time, frequently accompanied by projectile vomiting. The boy entered the hospital on July 19, 1939.

Examination.—The secondary sex characters were underdeveloped; cracked-pot percussion was elicited over the skull; the right pupil was larger than the left and did not react as well to light as the left; there was marked bilateral papilledema and a right homonymous hemianopsia. The deep reflexes were depressed, while the superficial reflexes were extremely active; there were no pathologic reflexes. His gait was somewhat awkward.

Laboratory Data.—Roentgen examination of the skull showed a moderate increase in the size of the sella turcica with thinning of the dorsum sellae. The bones of the calvarium were thin, and there was an increase in the digital markings suggesting increased intracranial pressure. No calcifications were seen. Serologic reactions were normal.

Course.—A few days after admission, moderate elevation of temperature was noted, but the pulse did not rise correspondingly, indicating some degree of pulse-temperature dissociation.[10] Perimetry showed a definite right homonymous hemianopsia. A lumbar puncture yielded cerebrospinal fluid under an initial pressure of 320 mm. of water; the final pressure was 140 mm. of water; the fluid was clear and contained no cells.

A neoplasm in the postchiasmal region, probably a suprasellar craniopharyngioma, was considered. Ventriculography was performed (July 25) and disclosed pronounced asymmetric dilatation of the lateral ventricles, the right lateral ventricle being larger than the left. There was dislocation of the septum pellucidum to the left. The third ventricle was not visualized. This, it was thought, indicated a tumor obliterating the third ventricle and impinging on the foramen of Monro on the right side. In the course of a left frontal craniotomy a tumor beneath the left optic nerve was exposed. During an attempt to remove this tumor with a curet a major hemorrhage occurred and caused termination of the operation. The patient died eight hours later.

9. Globus, J. H., and Globus, R. S.: Infundibuloma, a Newly Recognized Tumor of Neurohypophyseal Derivation with a Note on Saccus Vasculosus, J. Neuropath. & Exper. Neurol. **1**:59, 1932.

10. Globus, J. H., and Strauss, I.: Tumors of the Brain with Disturbance in Temperature Regulation, Arch. Neurol. & Psychiat. **25**:506 (March) 1931.

Necropsy of the Brain.—Gross Examination: The diaphragma sellae was deeply depressed and enlarged by a globular mass projecting from the floor of the third ventricle. The mass projected about 1.5 cm. beyond the surface of the base of the brain. Its anterior half was reddish black with an irregular, somewhat granular surface. Its posterior half was white and had a smooth surface; it felt as if it were cystic, but there were firm areas in the posterior portion. The optic chiasm, anterior to the tumor, was displaced to the left, and the tumor seemed to have enveloped the left optic tract.

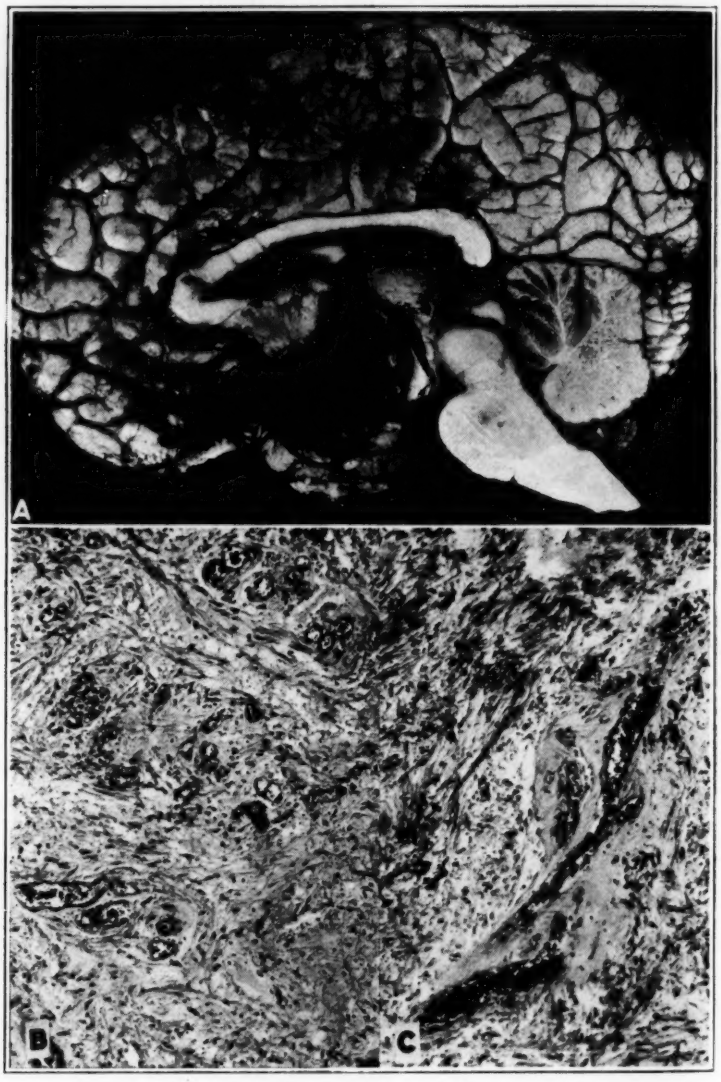

Fig. 18 (case 13).—*A*, sagittal section of the brain, showing the appearance and location of the tumor (infundibuloma); *B* and *C*, sections showing histologic structure of tumor (infundibuloma). Hematoxylin-eosin stain; *B*, × 64; *C*, × 80.

The brain was cut in the sagittal plane, and a tumor was found occupying the interpeduncular space (fig. 18 *A*). It was enveloped by what appeared at first glance to be a capsule; but on further study it was found that this was thinned brain tissue, probably remnants of the floor of the third ventricle. Having been thinned out, it displayed neither the marks of the tuber cinereum nor those of the mamillary bodies. This brain tissue, remnants of the floor

of the third ventricle, apparently had been displaced upward and to the right, as the bulk of the tumor was situated on the left side of the interpeduncular space. Further study disclosed that the tumor was embedded in the lateral wall of the third ventricle, in its hypothalamic portion. It could be easily enucleated and separated from a thin layer of tissue constituting the left lateral wall of the third ventricle. This layer of tissue, when traced rostrally and dorsally, was found thickened and adherent to the overlying fornix. At this point the tissue appeared neoplastic. When it was traced into the left hemisphere, the tumor was found to replace almost all of the structures in the interpeduncular space and to have become fused with the adjacent portions of the brain stem in the thalamostriatal area but separated from the hypocampal gyrus. The pituitary body was flattened and presented a pancake-rounded appearance.

Microscopic Examination: Throughout the tumor the cellular elements were predominantly elongated, unipolar or bipolar (fig. 18*B*). They were not unlike those found in the posterior lobe of the hypophysis, the pituicytes. The nuclei of the fusiform cells were centrally situated and were also elongated. The processes tapered off and were often undulated; not infrequently they were bifurcate. The unipolar forms had their nuclei at the base of the cell body. Often both the nuclei and the cell body were triangular in outline, and the cytoplasmic processes tapered off gradually. Particularly striking were the numerous vessels distributed throughout the tumor. Some of them had the dimensions of small capillaries or arterioles; four or more of them were often grouped together and were enveloped by a layer of supporting fine threadlike fibrous tissue. Other vessels exhibited features of large sinusoids lined by a single layer of endothelium. There were also what may be best described as vascular lakes, spaces limited by a faintly recognizable endothelial membrane. These were found to contain blood and some serum-like material. Most striking and characteristic were the vessels in the tumor, which were similar to those seen in the normal infundibular region, the so-called hypophysioportal vessels (fig. 19*C*). These were characterized by the wide zone of "gliogenous" investment which bordered on an endothelial lining. Among the cellular elements of the tumor tissue and in some of the vessel walls were seen numerous bodies which stained fairly well with eosin. They bore a strong resemblance to the colloidal substance or bodies found in the normal neurohypophysial region in and about the hypophysioportal vessels.

Special staining procedures, such as the Nissl, the Bielschowsky and the Globus modification of the Cajal gold sublimate (gold chloride–mercury bichloride) method, were employed in order to establish the presence or absence of neuronal and glial elements. Neither outspoken glial elements nor nerve cells could be found, except for an occasional disintegrated nerve cell. With the Hortega silver carbonate method the fusiform, bipolar and unipolar cell structures were well shown and their similarity to pituicytes well brought out.

Comment.—This case may be regarded as typical of cases of craniopharyngioma both clinically and anatomically. The location of the tumor at the crossroads of many significant tracts, near the crowded nuclear territory in the diencephalon and at a point on the course of many of the cranial nerves, readily explains the constellation of signs and symptoms in which corticospinal and cerebellar tracts, nuclei of the tuber cinereum and cranial nerves, particularly the second, third and sixth, participate. The diabetes insipidus and other vegetative disturbances are, of course, due to the involvement of the nuclei in the tuber cinereum. Variations in temperature when the pulse does not follow the rise and fall should arouse the suspicion of a lesion in this region.

SPONGIOBLASTOMA MULTIFORME

The wide assortment of primary tumors of the brain includes a large group of neoplasms of a type to which the name of spongioblastoma multiforme was given by Globus and Strauss.[4] The name was chosen for this form of tumor because of its cellular makeup, which consists predominently of unripe glial elements, the so-called spongioblasts. In all probability cells of greater or lesser differentiation are admixed with the cellular contents of such neoplasms. This is readily under-

stood when the accompanying chart relative to the mode of differentiation of the primitive neuroectoderm is consulted (fig. 19).

The original description of this type of tumor pointed to a primitive neuroepithelial cell, piriform in shape, often giving rise to a blunt process (fig. 20 *A*). Some of these processes come in contact with similar processes of neighboring cells, thus forming a reticulum. Many cells send their processes in a radial fashion toward blood vessels or cystlike spaces (fig. 20 *C*). Giant cells constitute a prominent feature of the spongioblastoma multiforme (fig. 20 *B*). They are found in large numbers, scattered through the microscopic field. They vary in size, shape and number of contained nuclei. In some of the cells the nuclei are gathered at one pole (fig. 21 *D*); in others they are arranged in a ring at the periphery of the cell, overlapping one another. In some cells the nuclei are connected with one another by fine chromate threads. The tumor is well vascularized, a condition which gives the gross specimen of the tumor a hemorrhagic appearance. Areas of necrosis alternate with the deep reddish brown islands seen on cross section of the tumor.

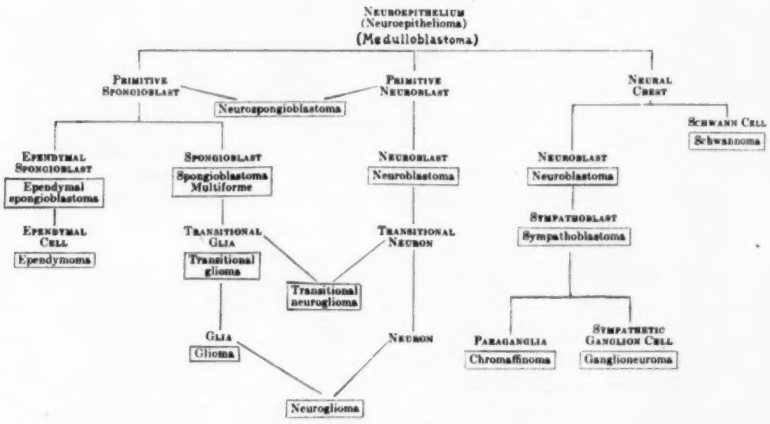

Fig. 19.—Schematic outline of the histogenetic stages in the development (maturation) of the neural, glial and ependymal elements of the nervous system with an indication of their relationship to the several forms of neoplasms neuroectodermal in derivation.

Spongioblastoma multiforme is the most common form of primary tumor in adults, while in children and adolescents it is relatively less frequent. In both age groups, however, it is a highly malignant, rapidly growing, recurring neoplasm. Clinically it is characterized by an acute onset, rapid progression and an almost always fatal course.

CASE 14.—*Spongioblastoma multiforme, a highly vascular and an unusually large cerebral neoplasm with an unusually short clinical history; death shortly after admission, and only one month after the onset of the illness; necropsy.*

History.—P. S., a girl aged 4½ years, was admitted to the hospital (Nov. 28, 1927) in a moribund condition. One month earlier she had begun to have twitching of the left extremities, daily vomiting and headaches. The parents then noted weakness of the left arm and leg, which became increasingly more pronounced. On the day of admission the child had a generalized convulsion and was immediately brought to the hospital.

Examination.—The child was in coma; the temperature was 107 F. There was a pronounced bilateral papilledema; the pupils were widely dilated and did not react to light; all the reflexes were absent. A lumbar puncture yielded uniformly bloody fluid.

Course.—The patient died in the reception ward. It was thought that a ventricular hemorrhage from a cerebral neoplasm had taken place.

Necropsy of the Brain.—Gross Examination: The brain was under increased tension; the convolutions of the right hemisphere were noticeably flattened. The temporal pole on the right side showed several cystlike structures, and the midbrain was pushed toward the opposite direction and was distorted. On sectioning of the brain, a large tumor was found in the temporoparieto-occipital lobe of the right hemisphere (fig. 21 *A*). It had almost completely replaced the basal ganglions on the right side, leaving a small part of the thalamus and corpus

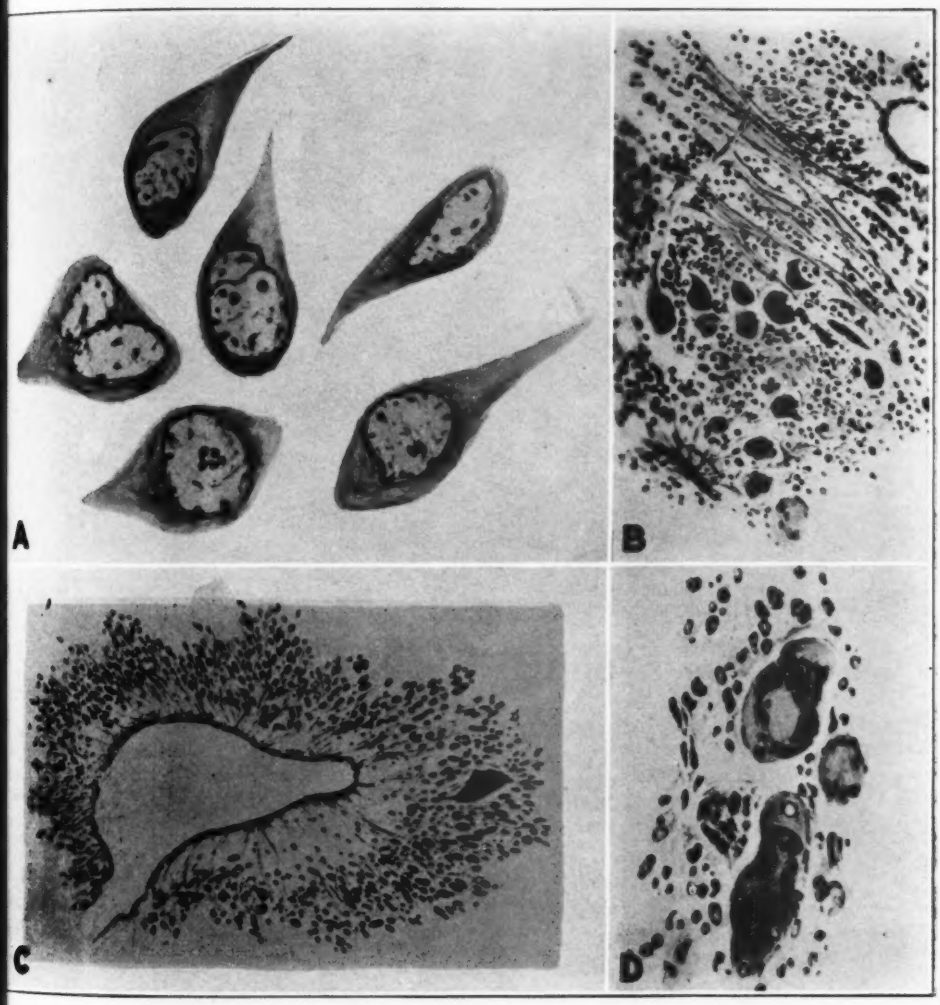

Fig. 20.—*A*, camera lucida drawing illustrating the distribution of the giant cells in spongioblastoma multiforme; *B* and *C*, camera lucida drawing showing giant cells and the radial arrangement of tumor cells with their processes directed to cystlike spaces; *D*, camera lucida drawing showing the character of giant cells in spongioblastoma multiforme.

striatum, and had displaced the descending and posterior horns laterally, reducing them to narrow slits. The tumor was granular and very vascular, with several zones of solid neoplastic tissue.

Microscopic Examination: Sections of the tumor revealed it to be extremely cellular, with a tendency for the cells to arrange themselves in rosette formations. There were numerous multinuclear giant cells with frequent mitotic figures and many thin-walled blood vessels (fig. 21 *B*). Necrotic areas were numerous and were often discolored by extravasated blood.

Comment.—This case is one of the few of supratentorial spongioblastoma. The acute onset and exceedingly rapid clinical course terminating in death are the common occurrence with tumors of this variety. This feature was emphasized by Elsberg and Globus [11] in a study of the so-called acute tumor of the brain.

Fig. 21 (case 14).—*A*, horizontal section of the brain, showing the location and character of the tumor (spongioblastoma multiforme); *B*, section showing the histologic appearance and the highly vascular nature of the tumor. Hematoxylin-eosin stain; × 130.

CASE 15.—*Spongioblastoma multiforme of the pons, extending into the cerebellum; a relatively long initial course, followed by an acute change with progressive decline; exploratory craniotomy; death; necropsy.*

History.—E. M., a girl aged 7½ years, was brought to the hospital on Feb. 16, 1925. She had been well until the age of 4½ years, when her parents noted that her left eye

11. Elsberg, C. A., and Globus, J. H.: Tumors of the Brain with Acute Onset and Rapidly Progressive Course, Arch. Neurol. & Psychiat. **21**:1044 (May) 1929.

turned outward and that she had a tendency to turn her head to the left. Her condition remained unchanged until three months before her admission to the hospital, when she became irritable and her gait became unsteady. She bled from the nose every few days and had recurrent episodes of vomiting; hearing in the left ear became impaired.

Examination.—The gait was slow, unsteady and broad based and was accompanied by a coarse tremor of the head. The fundi were normal. There were complete palsy of the left external rectus muscle with internal strabismus and weakness of the right internal rectus muscle. Nystagmus was present in all directions. The eyes were in conjugate deviation to the right. There was anesthesia of the left cornea. The jaw deviated slightly to the left. There were peripheral weakness of the left side of the face and nerve deafness, with absence of caloric responses on the left side. The tongue deviated slightly to the left and fibrillated. There were hypotonia, ataxia, past pointing and a bilateral Gordon-Holmes phenomenon, more marked on the left side. There were clumsiness and pseudoathetosis of the left hand. The deep reflexes were hyperactive, and there was a bilateral Babinski sign.

Course.—During the patient's stay in the hospital, papilledema developed and advanced; the vomiting continued. Exploration of the posterior fossa had to be interrupted because of the gravity of the child's condition. She died soon after, with signs of greater bulbar involvement.

Fig. 22 (case 15).—Coronal section of the brain stem and cerebellum, showing the character of the tumor (spongioblastoma multiforme and the pons and adjacent cerebellum).

Necropsy of the Brain.—Gross Examination: There was severe internal hydrocephalus. The floor of the third ventricle was bulging, extremely thin and translucent. The olfactory nerves were flattened; the third nerves were flattened and soft. The pons was deformed by an infiltrating mass, apparently intermedullary in origin, since it was covered by a normal glistening pia-arachnoid. The deformity was present mainly on the left side of the pons and extended down into the medulla as well as through the left cerebellar peduncle. The pons was exceedingly hard and voluminous. The same was true of the upper portion of the medulla, while the lower portion of the medulla adjacent to the cerebellar hemispheres was exceedingly soft. The fifth nerve was rather thin and flattened on the left side, while on the right side it was somewhat flattened; the sixth nerve on the left side was caught by the tumor mass; on the right side it was free, although somewhat thin. The eighth nerve on the left side was soft, displaced to the left, and lodged in a softened cystic area. The seventh nerve could not be found on the left side. On the right, the seventh and eighth nerves were found to be somewhat softened. On sectioning, the tegmentum of the pons was replaced by a reddish gray mass, which infiltrated the left middle cerebellar peduncle and extended into the adjacent portion of the cerebellum (fig. 22). The infiltrating mass extended down into the medulla. The fourth ventricle was reduced to an almost invisible horizontal slit.

Microscopic Examination: Section through the tumor mass showed a densely cellular, very vascular infiltrating neoplasm, with large areas of central necrosis. The cells were glial in type, with large central reticular nuclei and interlacing cytoplasmic processes. Numerous

mitotic figures were seen. An occasional giant cell and rosette formation was present. There were also scattered cells of a primitive glial type, with large amounts of cytoplasm and double or multiple nuclei.

Comment.—The clinical picture offered little difficulty in recognition of the character of the lesion and its location. The absence of papilledema during the earlier course is striking but not unusual for a pontile neoplasm, as will be noted from a review of all our cases with this localization.

The gross appearance of the tumor was typical of spongioblastoma multiforme. When compared with the appearance of medulloblastoma it will be noted that the difference was only in its greater invasion of adjoining structures.

SPONGIONEUROBLASTOMA

As experience with primary neuroectodermal tumors of the brain grew, particularly with the spongioblastoma multiforme, it soon became apparent that there is a large proportion of such tumors in which both glial and neuronal elements participate to an almost equal extent. The existence of such tumors could readily be accepted on theoretic grounds, since it is well known that the primitive neuroectoderm, the ultimate source of primary neuroectodermal tumors, is also the primordial material for the evolution of both glial and neuronal derivatives. Accordingly, Globus [12] assigned the name "spongioneuroblastoma" to this type of neoplasm, since both spongioblasts and neuroblasts contribute to its cellular population.

Spongioneuroblastoma presents some gross features which are quite characteristic. They are commonly associated with lesions of either a fully developed or an abortive form of tuberous sclerosis. They have as a fairly constant, but not exclusive, site of predilection the striatothalamic region. This, as recently postulated by Globus and Kuhlenbeck,[13] has as its reason the prevalence of embryonal rests in the subependymal cell plate along the sulcus terminalis. Histologically, the tumor cells are arranged in nestlike aggregations of spongioblasts and neuroblasts. Both types of cells vary in relative number and in the stages of their differentiation.

The fact that this type of tumor is associated with characteristic lesions of tuberous sclerosis would suggest the probability that it is a local accentuation of the neoplastic potency inherent in cells encountered in tuberous sclerosis.

CASE 16.—*Convulsive seizures in infancy; retarded intellectual development; cutaneous lesions (sebaceous adenoma); abrupt onset of manifestations of increased intracranial tension, headache, impaired vision, papilledema, meager localizing signs; ventriculography; coma; death; necropsy.*

History.—L. B., a girl aged 16 years, had had one brother who died in infancy of "convulsions" and a sister who succumbed to "brain fever" at the age of 2½ years. In addition to the common diseases of infancy, the patient was subject to convulsions during the period of dentition. For the last two years she had suffered from occasional cramplike pains in the calves. About seven months prior to admission persistent frontal headache developed, and shortly thereafter she noticed blurring of vision. After a short period of improvement, the headache increased in intensity and she was forced to give up work because of gradually increasing weakness. For the last two months it had been observed that she tilted her head backward and veered to the right when walking.

Examination.—The pupils reacted normally to light and in accommodation. There were bilateral exophthalmos and bilateral papilledema, more severe in the left eye. The corneal reflexes were diminished. There was a left central facial weakness. The deep and superficial

12. Globus, J. H.: Glioneuroma and Spongioneuroblastoma: Forms of Primary Neuroectodermal Tumors of the Brain, Am. J. Cancer **32**:163, 1938.

13. Globus, J. H., and Kuhlenbeck, H.: Tumors of the Aqueduct of Sylvius: Blastomatous Formations of Varied Origin, Limited to the Mesencephalon, J. Neuropath. & Exper. Neurol. **1**:207, 1942.

reflexes were active and equal. Hypotonia was present in both upper extremities. In walking the head was tilted to the left and the chin was carried to the right. There was a diffuse sebaceous eruption on the face (adenoma sebaceum). The visual fields were normal. Examinations of the blood, urine and serum revealed no abnormalities. Roentgenograms of the skull showed evidence of increased intracranial pressure. Intellectually the patient was somewhat retarded.

Course.—An expanding lesion in the posterior fossa was postulated, and, in view of the convulsive seizures, the cutaneous lesions and the retarded mentality, the diagnosis of tuberous sclerosis was considered. A patch near a blood vessel in the left fundus was observed on ophthalmologic examination and was regarded as a nodule not unlike that found in tuberous sclerosis. The patient returned home, and for nine months her condition remained unchanged. In the next three months she complained of progressive dimness of vision, vertigo, periodic

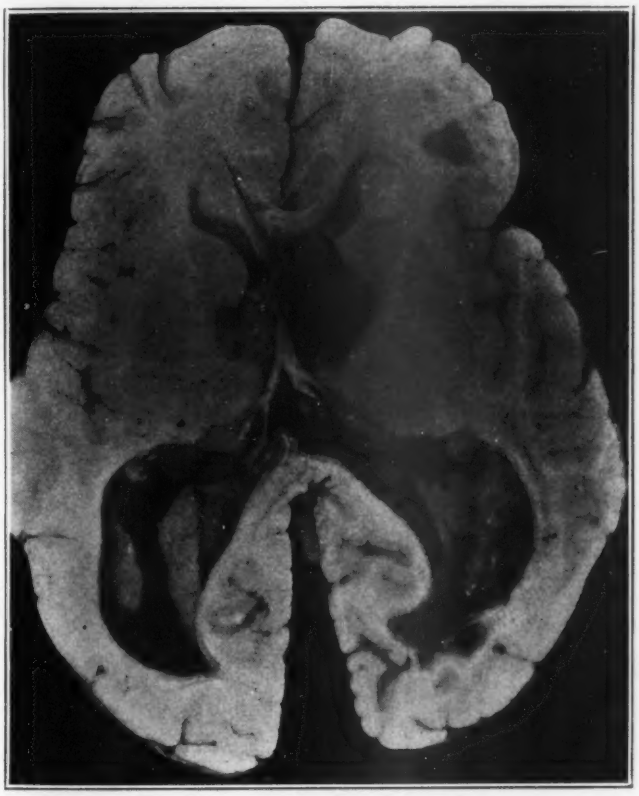

Fig. 23 (case 16).—Horizontal section of the brain, showing the location of multiple tumor nodules (spongioneuroblastoma) in the striatothalamic region.

vomiting and some vaguely described twitchings of the right upper extremity. She was readmitted to the hospital, where, in addition to the previous findings, she manifested a fixed facial expression and dilated pupils, the left practically fixed and the right sluggish to light. Her vision was greatly reduced. There was an equivocal Babinski sign on the right. The gait was uncertain, with a tendency to veer to the right. There was tenderness on percussion over the left temporoparietal region of the skull. Ventriculography was performed, and several hours after this procedure the patient was found in a comatose and deeply cyanotic condition. She died the next day.

Necropsy of the Brain.—Gross Examination: The brain showed evidence of increased intracranial pressure. Palpation revealed numerous areas of the cortex which were hard and nodular. A tumor was found in the region of the right thalamus, almost completely replacing the anterior two thirds of that structure on the right side (fig. 23). The tumor was brownish red, measured 2.5 cm. in the anteroposterior diameter and extended downward as far as the

massa intermedia, compressing the third ventricle from above downward. A similar and much smaller mass was found in the mesial portion of the left thalamus. A smaller rounded mass, about 7 mm. in diameter, was found in the region of the left pulvinar, projecting into the body of the left lateral ventricle. The cerebral cortex was extremely irregular in width; in some areas, as under the flattened and hardened tuberous areas, it was almost completely obliterated. The ventricular cavities, including all the compartments of the lateral ventricles,

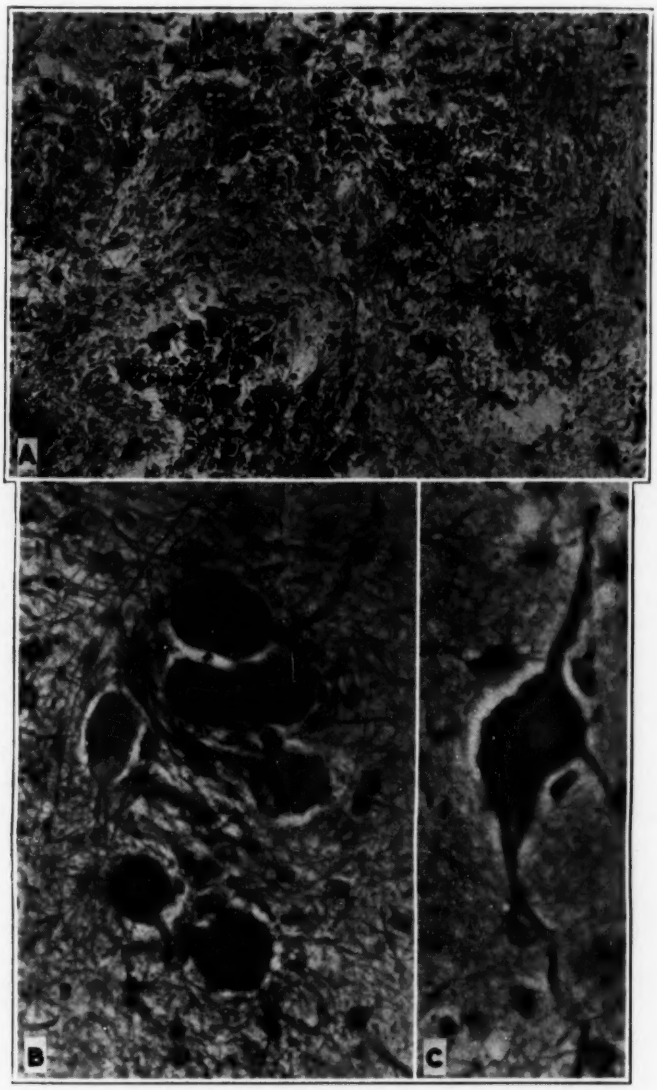

Fig. 24 (case 16).—*A*, section of the tumor, displaying nestlike aggregations of the tumor cells. Globus modification of Hortega variant I stain; × 66; *B* and *C*, monster giant cells in tuberous nodudes found in parts of the brain remote from the tumor. Globus modification of Hortega variant I stain; × 275.

were distended and filled with bloody fluid. The third ventricle in its upper part was reduced to a narrow slit by the two opposing tumors. The ventricular lining was thickened and was studded with numerous granulations.

Microscopic Examination: Sections throughout the tumor presented a characteristic histologic appearance. The tumor cells were arranged in nestlike aggregations separated by strands of myelinated fibers (fig. 24 *A*). Among the tumor cells were many giant cells, some

of which when stained by Nissl's method displayed their neuronic character. The alterations in the cerebral hemispheres were typical of those of tuberous sclerosis. The thickening and gliosis of the tangential layer and the tuberous nodules with collections of atypical spongioblasts and neuroblasts were numerous and conspicuous (fig. 24 *B, C*).

Comment.—The family history, the convulsive seizures in the early life of the patient, the cutaneous eruption on the face and the small retinal nodule were of great value in diagnosis; but the diagnosis was somewhat obscured by the fact that the symptoms and signs of increased intracranial tension, such as impaired vision, papilledema and the roentgenographic findings, pointed to the existence of a circumscribed intracranial tumor. The anatomic findings in this case included abundant evidence that the generalized lesion was in the nature of tuberous sclerosis, in which a local intensification of the process resulted in the formation of a large tumor and provoked the symptoms of increased intracranial tension.

TRANSITIONAL GLIOMA AND GLIONEUROMA

It is a frequent experience to find primary neuroectodermal tumors of the brain the histologic character of which defies accurate identification because of the wide range of differentiation of their cellular components. The practice in naming tumors is to discover the dominant type of cell. But this is not always possible, for there are tumors in which the bulk of the neoplastic tissue may be in a state of transition from the primitive form of cell to the differentiated type. Under such circumstances the term transitional glioma, if the tumor is dominantly glioblastic, or transitional glioneuroma,[14] if both glia and fairly mature nerve cells are equally represented in the tumor, is well suited.

CASE 17.—*A pontile, transitional glioma with rapidly progressive clinical course in a young child; onset of symptoms marked by history of trauma; no surgical intervention; death; necropsy.*

History.—J. K., a girl aged 3½ years, was apparently well until eight weeks before entering the hospital. Her fatal illness was said to have been ushered in by a fall from a carriage. She was struck by the falling carriage over the left side of the face. She lost consciousness, and a generalized convulsion which lasted about twenty minutes developed. She regained full consciousness but remained irritable and cried a good deal during the week following the accident. A physician observed paralysis of the right side of the face, drooping of the left eyelid and inability to turn her right eye upward. Three weeks after the initial episode, the child's gait became unsteady and she occasionally fell. She became disinclined to use her left hand and arm, and her left leg appeared to be weak. During the next five weeks she gradually became listless and continually asked for food or water. She was severely constipated and vomited once.

Examination.—The patient was extremely dull. The right pupil was larger than the left. There was palsy of the right oculomotor and of the left abducens nerve, with loss of conjugate movement of the eyes to the right. A peripheral weakness of the left side of the face, a left hemiplegia with hyperactive deep reflexes and a positive Babinski sign on the left side were the other neurologic findings.

Course.—In view of the history of trauma the diagnosis of massive hemorrhage into the pons and small hemorrhages scattered throughout the cerebral hemispheres was considered. The child's condition remained unchanged for a while, but during the fifth week in the hospital she began to vomit repeatedly and early papilledema was observed for the first time. The cerebrospinal fluid pressure, which had been normal, was now elevated and was found to be initially 160 mm. of water. The papilledema and increased intracranial tension aroused the suspicion of a tumor in the pons, but surgical intervention was considered inadvisable. She declined rapidly and died within the next two weeks.

Necropsy of the Brain.—Gross Examination: The entire brain stem was enlarged and felt cystic. This was especially true of the right side of the basis pontis and the midbrain. An excrescence which also felt soft and cystic, about 1 cm. in diameter and with a bluish

14. Levin, G.: Some Transitional Gliomas, Am. J. Cancer **35**:22, 1939.

color, was noted in the ventral portion of the right side of the medulla just below the cerebellopontile angle. Sectioning of the brain in the upper portion of the pons disclosed a large cyst in the midline, directly beneath the ependyma of the fourth ventricle (fig. 25 *A*). It was filled with a greenish brown material. In the center of the cut section there was a small hemorrhagic area, about 1 cm. in diameter. The entire cut section appeared discolored by hemorrhage.

Microscopic Examination: The tumor exhibited a rather cellular and vascular structure. The cell elements were arranged in small nests usually surrounding a blood vessel and in interlacing cellular streams. The more or less dense cellular material bordered on a large area of extravasation with blood vessels undergoing degeneration. The cells when studied by means of special stains appeared to be in various stages of glial maturation. Common among these cells were the exceedingly long, fusiform, bipolar spongioblasts (fig. 25 *B*). There were many giant cells with overlapping nuclei.

Comment.—Note was taken of the history of trauma to the head, but, as will be shown later, it was an event which need not be considered as a contributing factor in the clinical course. It, however, served to mark the time of onset of the more

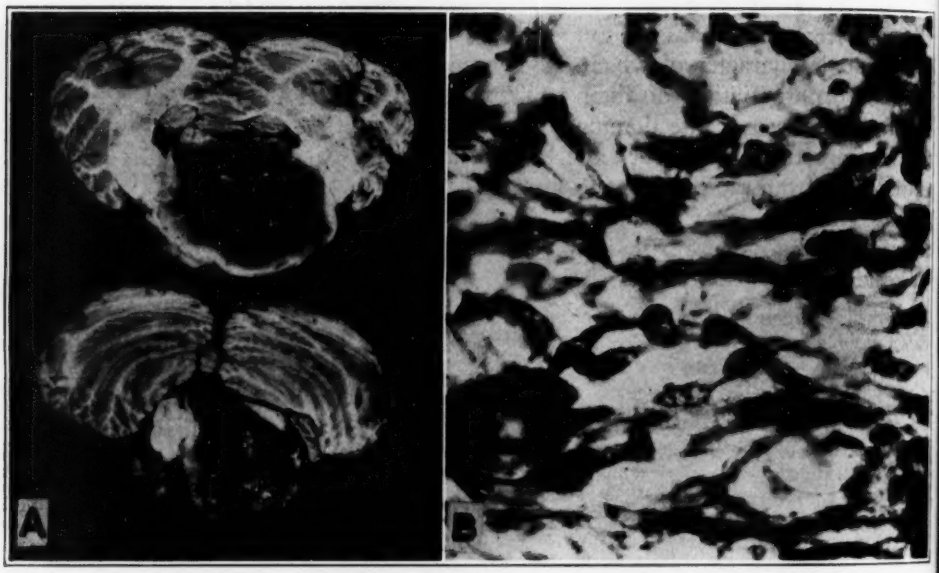

Fig. 25 (case 17).—*A*, coronal sections of the brain stem, showing the location and appearance of the pontomedullary tumor; *B*, section of tumor, displaying the histologic character. Globus modification of Hortega variant III stain; × 167.

obvious symptoms, which had probably manifested themselves in a milder form earlier in the life of the patient but had passed unobserved.

CASE 18.—***Recurrent convulsive seizures; gradual mental deterioration; fatal end in status epilepticus; necropsy.***

History.—V. M., a white woman aged 22 years, had had a series of generalized convulsions for the first time at the age of 16 years. Since then she had had convulsive seizures daily. They varied in intensity and duration. At times they had the character of petit mal attacks, and at other times they were generalized tonic-clonic convulsions accompanied by loss of consciousness. In 1922 an associated psychosis brought the patient to a state hospital. She remained there three years; her condition improved, and she was allowed to return home. Three days prior to admission to this hospital she passed through a series of severe convulsive attacks; she became dull and apathetic.

Examination.—The pupils were unequal, the right larger than the left. The deep reflexes were increased on the left side, and there was a bilateral Chaddock sign.

Course.—Shortly after admission to the hospital she had a tonic convulsion with deviation of the eyes to the right. These seizures recurred almost hourly for the next two days. A

lumbar puncture was performed and showed the cerebrospinal fluid under increased pressure. The patient lapsed into stupor; status epilepticus developed, and she died on the fourth day in the hospital.

Necropsy of the Brain.—Gross Examination: The brain was voluminous; the gyri were flattened, and the leptomeninges showed an area of discoloration over the occipital lobe. On incision a large neoplastic mass was found replacing almost the entire right temporal lobe and a large part of the right occipital lobe (fig. 26 *A*). It displaced the inferior frontal

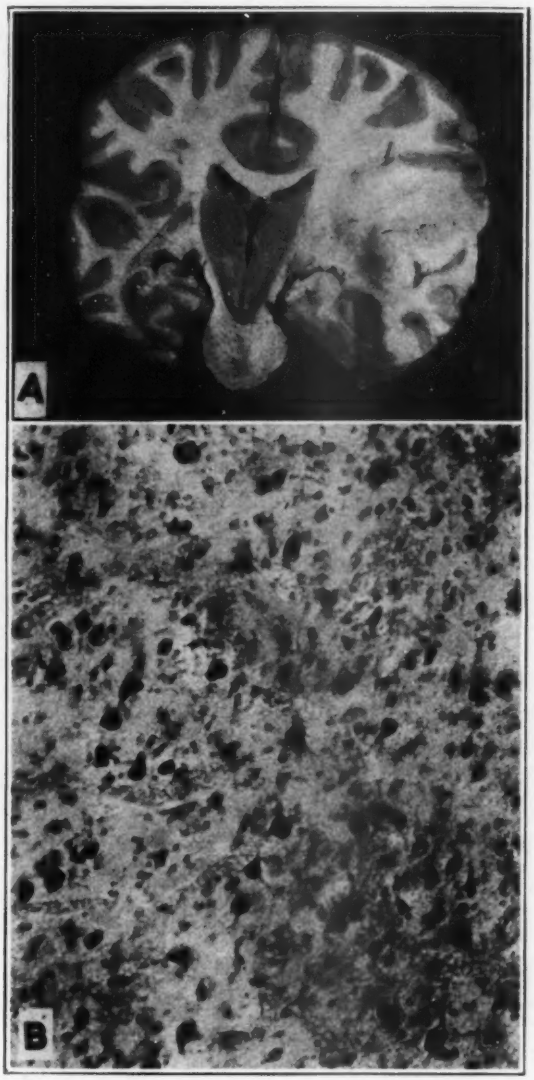

Fig. 26 (case 18).—*A,* coronal section of the brain, showing the marked hypertrophy of one hemisphere, the seat of a diffuse tumor; *B,* histologic character of the tumor exhibiting the structure of transitional glioneuroma. Nissl stain; × 163.

convolution upward. It extended rostrally as far as the temporal pole, while caudally it reached the middle of the occipital lobe; it invaded the island of Reil and the corpus striatum. The tumor was somewhat soft but tenacious, smooth and yellowish and contained a few cysts in its depth. It was poorly demarcated from the surrounding normal tissue. The right ventricle was compressed, while the left was dilated.

Microscopic Examination: The gradual transition of the tumor into the apparently normal cortex made it difficult at first to recognize the fact that the neurons were tumor cells. The first impression was that the cells were either extensions from the normal cortex or that the cells of the normal cortex were caught in the midst of an invasion by neoplastic glial elements; but the small size of the neuronal elements, their incomplete maturation and their close resemblance to similar cells in other glioneuromas (fig. 26 *B*), as well as their distinct difference from the neurons in the normal cortex, made certain their neoplastic origin. Moreover, the background of neoplastic glia cells added further proof of their blastomatous character. By special staining methods these glial elements could be recognized as distinct and fairly well differentiated astrocytes. An embryonal pattern of the vascular channels was observed, as well as many cystlike defects.

Comment.—Here again the clinical events and anatomic findings pointed to a slowly progressive blastomatous process which probably had been incipient in the brain from its early period of development. The neoplasm also bore a strong resemblance to the larger group of blastomatous malformations, the so-called tuberous sclerosis.

EPENDYMOMA

With the understanding that the ependymal cells lining the several ventricles of the brain and those clothing the choroid plexus have a common source of origin, it is quite reasonable to assume that tumors with their dominant cell type of ependymal variety, no matter what their location and stage of cellular differentiation, belong to a common neoplastic form, ependymoma. This has been made clear by Kernohan,[15] who, however, suggested a subgrouping into several forms of ependymoma on one hand and papilloma of the choroid plexus on the other. Such grouping may have some advantages, but it is obtained at the risk of obscuring the fact that the tumors classified as different types represent only different stages in the differentiation of their cellular components.

It is difficult to describe the histologic character or gross appearance of any ependymoma which can be regarded as typical of the entire group, so numerous are the variants. Generally the cells simulate normal ependymal cells by their cuboidal or low columnar forms and by their tendency for a cordlike arrangement. In some instances the cellular organization simulates that of a mature choroid plexus.

The gross features of the tumor are not striking beyond their intraventricular location. Often the growth spreads into subependymal and deeper parts of the brain adjacent to the ventricles, but occasionally it may for its greater part be attached to the brain substance only by a peduncle. It is the latter condition that gave rise to the older view that ependymoma is benign. This does not, however, hold in the light of more recent experience.[16] In some instances, even when the component cells are of the mature variety, the tumor is malignant because of its invasion of the adjacent brain tissue. Thus, the intraventricular location of the growth, though it may be benign histologically, favors successful surgical intervention only in rare cases.

CASE 19.—*Ependymoma of the choroid plexus, papilloma variety; short clinical course; invasive ventricular tumor found at necropsy.*

History.—J. R., a 14 month old boy, was brought to the hospital on May 29, 1928. Several weeks after he had undergone a mastoidectomy (right side) the child had become alternately listless and irritable. He vomited repeatedly and daily.

Examination.—There was pronounced hydrocephalus; the eyeballs were turned upward and to the right; the pupils reacted poorly to light. There was paresis of the left side of

15. Kernohan, J. W., and Fletcher-Kernohan, E. M.: Ependymomas, A. Research Nerv. & Ment. Dis., Proc. (1935) **16**:182, 1937.

16. Weinstein, E. A.: Ependymomas Arising from the Ventricular Lining and Choroid Plexus, J. Mt. Sinai Hosp. **5**:573, 1938.

the face, and the deep reflexes were more active on the left side. A lumbar puncture yielded clear cerebrospinal fluid under increased pressure.

Course:—The child died several days after admission of pneumonia.

Necropsy of the Brain.—Gross Examination: The lateral and the third ventricles were dilated. Within the posterior horn of the right lateral ventricle there was a brownish friable tumor mass. Extending from that mass and from the adjacent brain tissue to which it was attached there was a wide zone of discoloration which followed the outlines of the lateral

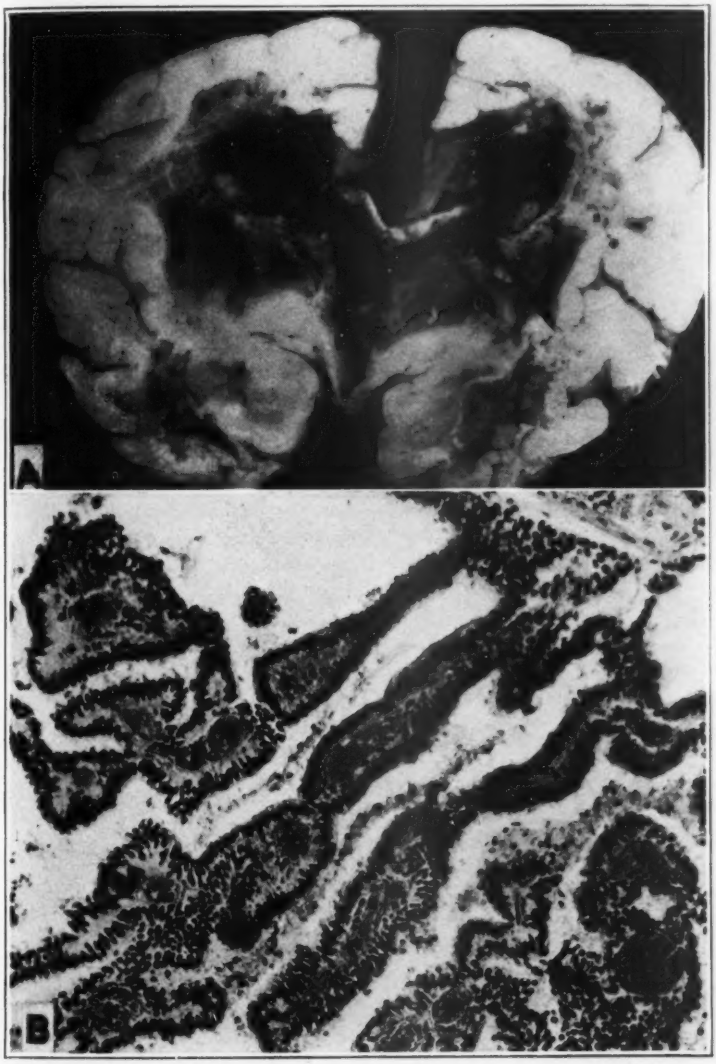

Fig. 27 (case 19).—*A*, coronal section of the brain, showing the location of the tumor, indicated by the areas of discoloration; *B*, section showing the histologic character of the tumor, displaying a structure similar to that of the choroid plexus. Hematoxylin-eosin stain; × 136.

ventricles on both sides of the brain (fig. 27 *A*) and also that of the third ventricle. This on histologic study was found to be tumor tissue.

Microscopic Examination: The tumor consisted of numerous villus-like projections, coated by low columnar epithelium, and containing a core of connective tissue often vascularized by thin-walled capillaries (fig. 27 *B*) or larger blood vessels. In general, it duplicated closely the structure of a fully developed choroid plexus.

Comment.—It is rather remarkable that in a child of only 14 months the tumor should have acquired such a differentiated character. However, we have found a similar situation in patients with other types of tumor, particularly pinealoma, in whom the tumor showed a higher cellular differentiation and organization in younger patients than in older ones.

This case offers little in the way of clinical information, since the patient was under observation only a few days and was not subjected to any special tests.

CASE 20.—*Invasive ependymoma of the undifferentiated variety, widespread in distribution along the ventricular lining; tumor diagnosed; craniotomy, with partial removal; rapid fatal termination; necropsy.*

History.—P. T., a boy aged 3½ years, was apparently well until three months before admission to the hospital (Nov. 24, 1939). At that time he began to vomit frequently, and two weeks later headaches developed, more on the right side and especially severe in the morning. Later his gait became unsteady, and he became increasingly drowsy. Impaired vision in the right eye and asymmetry of the face, with his mouth drawn up on the right side, developed shortly before he was brought to the hospital.

Examination.—There was a suggestion of hydrocephalus with slight parietal bossing and slight tenderness to percussion on the left side of the skull. The right eye revealed primary atrophy of the optic nerve, while the left disk was choked. The pupils were dilated and unequal, the left being larger than the right. There was a suggestion of a left homonymous defect in the visual fields on confrontation. Left hemiparesis, including the face, absence of abdominal reflexes on the left and a Babinski sign elicited on the right, unsteady gait with loss of associated swing of the right arm, posturing of the head to the left and a marked tremor of the left upper extremity completed the clinical picture.

Laboratory Data.—Roentgen examination of the skull showed moderate increase of digital markings and separation of the sutures. A ventriculogram revealed the left lateral ventricle to be dilated and displaced to the left, while the right lateral ventricle could not be visualized.

Course.—A tumor of the right temporal lobe was diagnosed, and a craniotomy was done immediately after the ventriculography (December 5). A large vascular tumor of the right frontal lobe extending posteriorly was found and partly removed. The patient died a few hours after operation.

Necropsy of the Brain.—Gross Examination: On sectioning, almost the entire superior two thirds of the temporal lobe was missing and the part which was left intact presented a granular surface suggestive of being infiltrated by tumor tissue. Part of the inferior frontal convolution adjacent to the defective right temporal lobe showed disorganization and softening (fig. 28 *A*). The ventricular system was dilated, particularly on the contralateral side, while the ipsilateral lateral ventricle was somewhat elevated. This part and the bodies of both lateral ventricles were filled with coagulated blood. The brain stem on the side of the tumor was compressed and deformed. The septum pellucidum was partly disorganized, having been reduced to a small mass of soft tissue. The ependymal lining of the ventricles in that region was coated with a brownish material. The choroid plexus of the descending right ventricle was somewhat soft. The tumor measured 7½ by 4 by 5 cm. On sectioning, the tumor presented a granular surface with islands of grayish tissue surrounded by larger areas of pinkish tissue, enclosing in the center a fairly large oval hemorrhagic area.

Microscopic Examination: Sections of the tumor revealed densely cellular neoplastic tissue. The cells were rather uniform in size, possessed darkly staining, relatively large, round nuclei surrounded by a large amount of cytoplasm. The cells were arranged in cords simulating the structure of a gland of internal secretion (fig. 28 *B*). There was a considerable amount of necrotic alteration in the tissue, and the neoplastic cells showed a tendency to group themselves about such areas. At some points at the periphery there were groups of mature glia cells resembling astrocytes. The tumor was very vascular, the blood vessels varying considerably in size. They were congested, and many contained thrombi. Apart from displaying an argentophilic reticulum in the tumor, the special silver and gold preparations did not yield any new evidence.

Comment.—This tumor, while belonging to the general group of ependymomas, presented features of the less differentiated type of neoplasm. It would, according to Kernohan, belong to the cellular form of ependymomas. It is unfortunate that the majority of these tumors are so invasive, particularly when encountered in the young, for they offer no hope for successful surgical intervention.

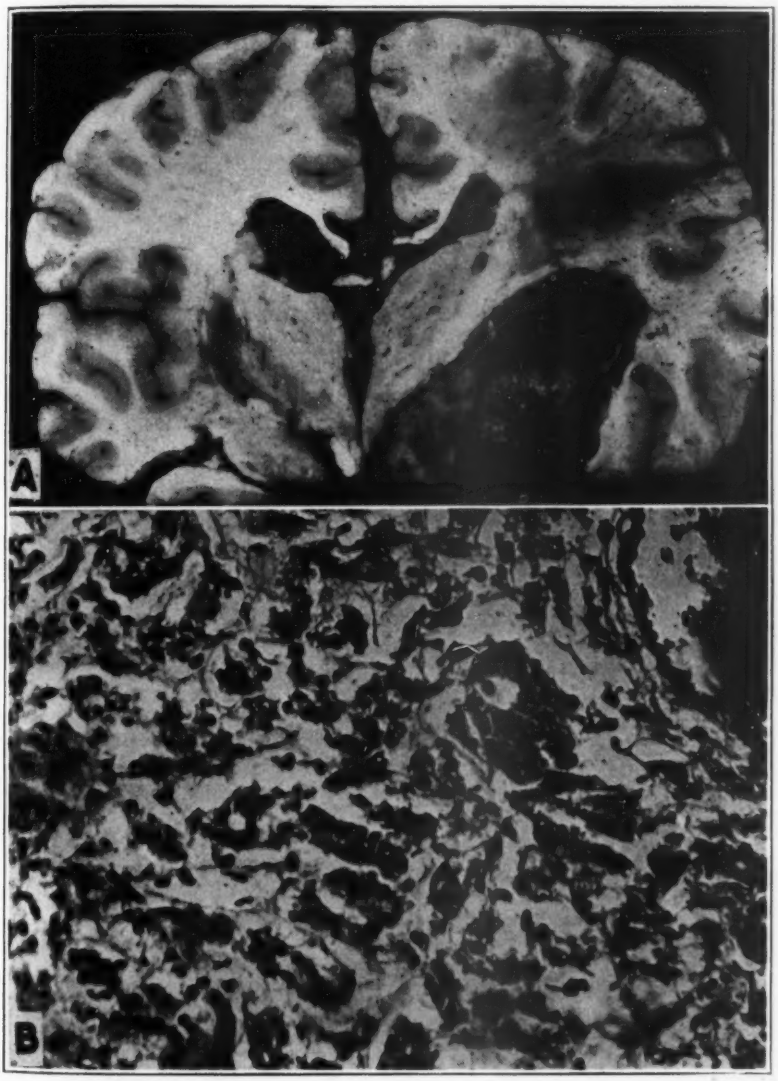

Fig. 28 (case 20).—*A*, coronal section of the brain, showing the location of the tumor in the descending horn of the right lateral ventricle; *B*, section showing the cell form (ependymal) constituting the dominant cellular element of the tumor. Hematoxylin-eosin stain; × 289.

TUBEROUS SCLEROSIS

The clinical manifestations of typical tuberous sclerosis are well known. The triad of symptoms, convulsive seizures, retarded mental development and the characteristic cutaneous eruption (adenoma sebaceum), insures clinical recognition. But

there are instances in which the disease, either in an infant or in an adult, defies diagnostic efforts. Either it lacks one or more of the cardinal signs and symptoms or its true character is obscured by manifestations due to an added factor, an expanding lesion. Since the original studies of Bourneville [17] and Hardtegen,[18] important observations have been made on the pathogenesis of the disease. The consensus is that it is a developmental anomaly, with blastomatous potencies on the part of the gliogenous and, it may be added, neuroblastic elements of the nervous system. It is assumed that embryonal glia and nerve cells are, so to speak, derailed from the normal course of growth and differentiation. These cells, endowed as they are with potencies for growth and differentiation, retain, therefore, neoplastic tendencies which are released under abnormal circumstances. This leads to focal development of smaller or larger tuberous nodules, some acquiring the size of a

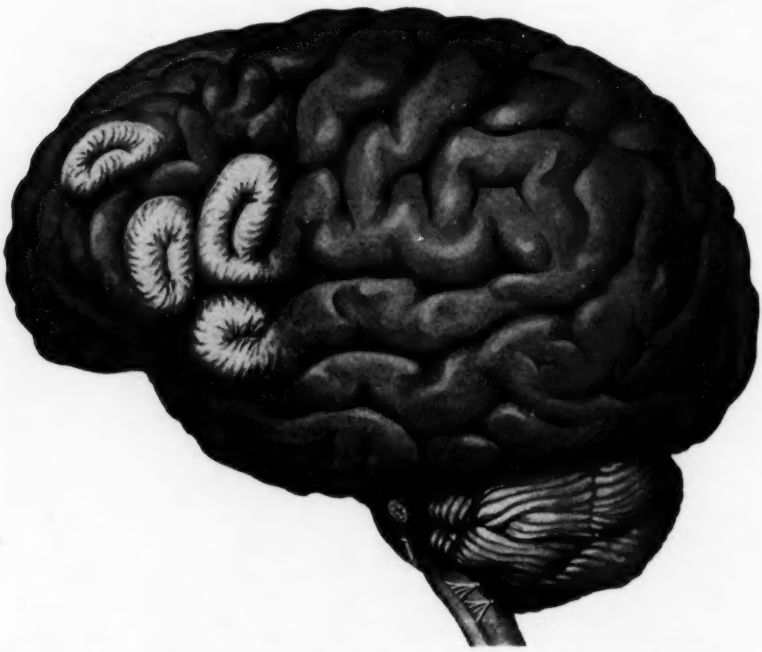

Fig. 29 (case 21).—Drawing of the lateral surface of the brain, exhibiting a number of tuberous nodules.

tumor. The latter explains the frequency with which tuberous sclerosis is associated with spongioneuroblastoma.[12]

CASE 21.—*Tuberous sclerosis in an infant; sudden onset, followed by a rapidly fatal course; undiagnosed; necropsy.*

History.—J. V., a boy aged 5 months, was apparently normal at birth. His development was normal, and he seemed to be well until twelve hours before admission to the hospital, when he suddenly was seized with a series of generalized convulsions. Each attack lasted about one hour, and the seizures recurred at hourly intervals.

Examination.—The child, aside from signs of rickets, presented no abnormalities. All the deep reflexes were present. The temperature was normal.

17. Bourneville, D. M.: Sclérose tubéreuse des circonvolutions cérébrales, Arch. de Neurol. **1**:87, 1880.

18. Hardtegen, A.: Ein Fall von multiplen Verhaertungen des Grosshirns, Arch. f. Psychiat. **11**:117, 1880.

Course.—Bromides and chloral hydrate administered by rectum reduced the frequency of the attacks. On the second day in the hospital his temperature rose from 102 to 103 F., and purulent conjunctivitis and fulness of the right ear drum were noted. Two days later, a thin, scant discharge emerged through a small perforation in the right tympanic membrane and slight fulness of the left ear drum was noted. These conditions were not regarded by the otologist as sufficient cause for the rise in temperature. At this time the facial expression of the child and a tremor of the upper extremities, together with positive Chvostek and Trousseau signs, suggested the diagnosis of tetany. The calcium content of the blood was 7.8 mg. per hundred cubic centimeters. The Wassermann reactions of the

Fig. 30 (case 21).—Nodule of tuberous sclerosis exhibiting a number of monster glial cells with numerous processes. Globus modification of Hortega variant I stain; × 208.

blood and cerebrospinal fluid were negative. The differential blood count was normal. In view of the steadily rising temperature a culture of the blood was made, but organisms were not isolated. The convulsive twitchings continued. A calcium preparation (calcium chloride urea [afenil]) was then injected into the superior longitudinal sinus, and the twitchings ceased for a few hours. On their recurrence sedatives were administered by mouth and by rectum without effect. The child died four days after the onset of the illness.

Necropsy of the Brain.—Gross Examination: Palpation of the surface of the brain disclosed gyri which presented marked hardness. One was located in the left frontal lobe;

another, slightly larger, in the left parietal lobe; another, in the left temporal lobe, and still another, in the right parietal lobe (fig. 29). On sectioning of the brain, these hard nodules showed a loss of the normal demarcation between the gray and the white matter.

Microscopic Examination: Sections obtained from the several discrete tuberous (nodular) areas exhibited, even with low magnification, alterations in the architecture of the involved cerebral cortex. The normal lamellation of the cerebral cortex was disturbed to a considerable degree by the presence of many overdeveloped or undifferentiated glia and nerve cells and by the reduction in the number of the nerve cells. In the tangential zone, dense bundles of glia fibers were found entering the pia in a brushlike arrangement. A still more distinguishing feature of the nodules was the monstrous giant cells which, singly or in groups, were distributed irregularly in the gray or subjacent white matter (fig. 30). Most often their glial or neuronic origin could be identified by special staining methods. However, with the aid of the silver and the gold sublimate method, the glial character of some of the giant cells could readily be established. The unusual wealth of fine filamentous processes and the enormous length of these processes were well demonstrated in such preparations. The neuronic origin of some of the giant cells was demonstrated also in preparations stained by the Bielschowsky method. In such preparations the fibrils in the cytoplasm and the clear nucleus and darkly stained nucleolus helped to identify the character of the cells. In contradistinction to the monster glia cells, the nerve cells presented short, blunt processes at irregular points of the cell body. Vacuoles in the cell bodies were often seen; they probably indicated degeneration of the cells. It was often difficult to distinguish between the glia and the nerve cells, for there were cells in which the staining methods did not reveal features which would make possible such a distinction. The cells, though resembling nerve cells in shape and character of processes, displayed no intracellular fibrils. Many of the giant cells had grotesque outlines and processes of enormous length, which are not seen in any other pathologic condition.

Comment.—The only neurologic manifestation of significance in this case was the convulsive seizures. They, however, represented only one of the triad of signs and symptoms typical of tuberous sclerosis. The age of the child made it difficult to estimate the intellectual level, and the absence of cutaneous lesions removed another guide to the correct diagnosis. Moreover, few cases of tuberous sclerosis in infants have been recorded in the literature.[19] Thus, it would seem one can do little more than suspect tuberous sclerosis in an infant with recurrent generalized convulsions occurring over an extended period.

CASE 22.—*Progressive loss of vision followed by evidence of increased intracranial tension; exploratory craniotomy without disclosure of tumor; obstruction in third ventricle disclosed by a ventriculogram; second craniotomy, part of tumor removed; rapid decline; death; necropsy; tumor arising in mamillothalamic bundle disclosed.*

History.—C. W., a girl aged 14 years, entered the hospital complaining of progressive loss of vision in the right eye for six months and of headaches, vomiting and tinnitus in the left ear for three months. During the last two weeks vision in the left eye had become blurred.

Examination.—On admission, the following conditions were disclosed: papilledema of the left disk and atrophy of the right optic nerve; slightly dilated pupils, the right being fixed to light and the left responding very little to light; bilateral exophthalmos and a slight right external squint; a slight weakness of the left side of the face; some impairment of hearing on the right side, and some weakness and moderate astereognosis of the left hand. Her memory was poor. There were numerous pigmented spots on the arms and trunk. A lumbar puncture yielded clear cerebrospinal fluid under an initial pressure of 300 mm. of water.

Course.—Encephalography was attempted, without satisfactory results. An exploratory right frontal craniotomy was performed (July 5, 1930), but no tumor was found. Ventriculography was done two weeks later, and indigo carmine was injected into the left ventricle. The dye promptly appeared through the needle inserted in the other ventricle. Air was injected, and the lateral ventricles were well outlined and large, but only the optic recess of the third ventricle was visualized. A craniotomy for a tumor in the third ventricle

19. Globus, J. H., and Selinsky, H.: Tuberous Sclerosis in the Infant, Am. J. Dis. Child. **50**:954 (Oct.) 1935.

was then carried out. A small hard tumor mass was found in the optic recess and was partly removed. After the operation the patient remained in a semistupor and died two days later.

Necropsy of the Brain.—Gross Examination: The brain was removed through the surgical defect in the skull. It exhibited severe bilateral internal hydrocephalus and a hard mass measuring about 2 cm. in diameter invading the anterior and lower portions of the third ventricle. The tumor mass was irregular in outline, and its long axis was on the horizontal plane. Its lower edge was directly above the tuber cinereum. Careful dissection disclosed it to be adherent to a fibrous tract leading from the mamillary body to the thala-

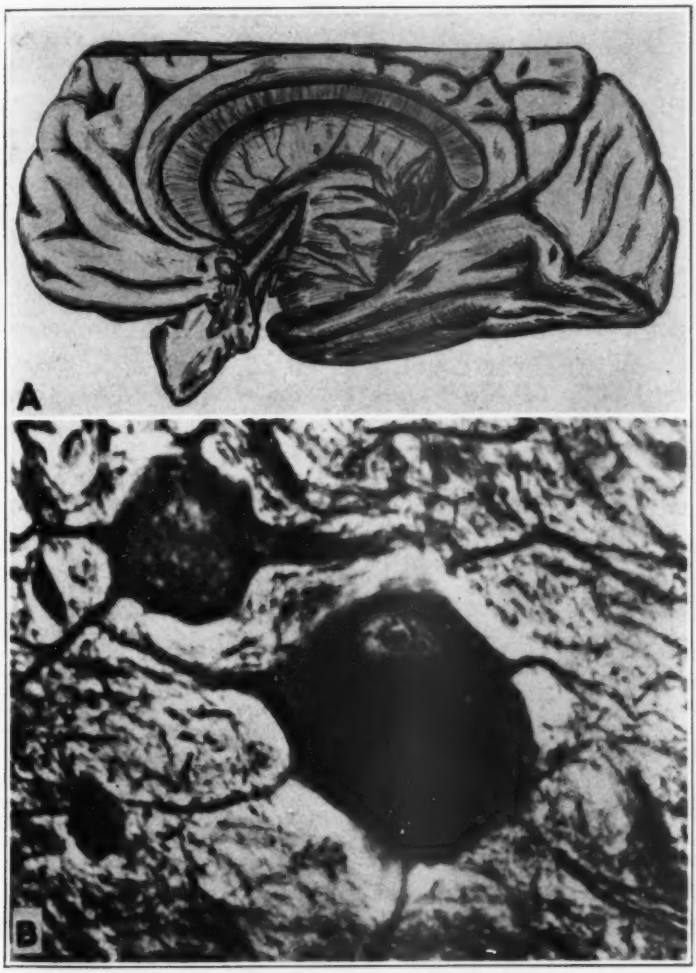

Fig 31 (case 22).—*A*, drawing showing remnant of a tumor attached to the mamillothalamic bundle; *B*, monster nerve cells in an area remote from the site of the tumor. Globus modification of Hortega variant I stain; × 192.

mus (the mamillothalamic bundle [fig. 31]). It was hard and pearly white. In the region of the lobus quadratus and in the superior parietal lobule there were found small nodular areas which were somewhat flattened, of harder consistency and of a lighter hue in comparison with the adjacent parts of the gyri, recalling the nodules seen in tuberous sclerosis.

Microscopic Examination: Sections of the tumor stained by the usual histologic methods and examined with low magnification revealed the typical features of a neurinoma. There was the characteristic palisading of nuclei, paralleling numerous fibers arranged in sheaths or bundles, running in various directions and often interlacing. Most of these fibrous bundles crossed the microscopic field in a longitudinal direction; others, apparently cut across,

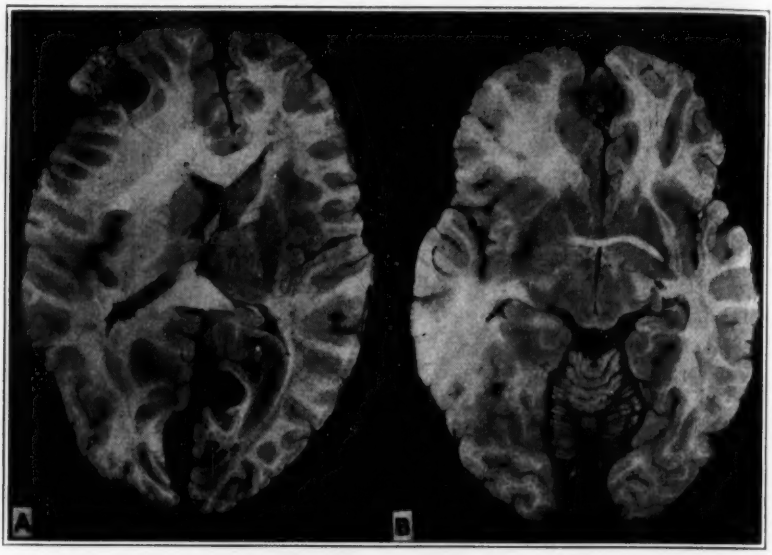

Fig. 32 (case 22).—Horizontal section of the brain, showing several tumor nodules, one in the prefrontal area on the lateral aspect and another in the region of the longitudinal fissure.

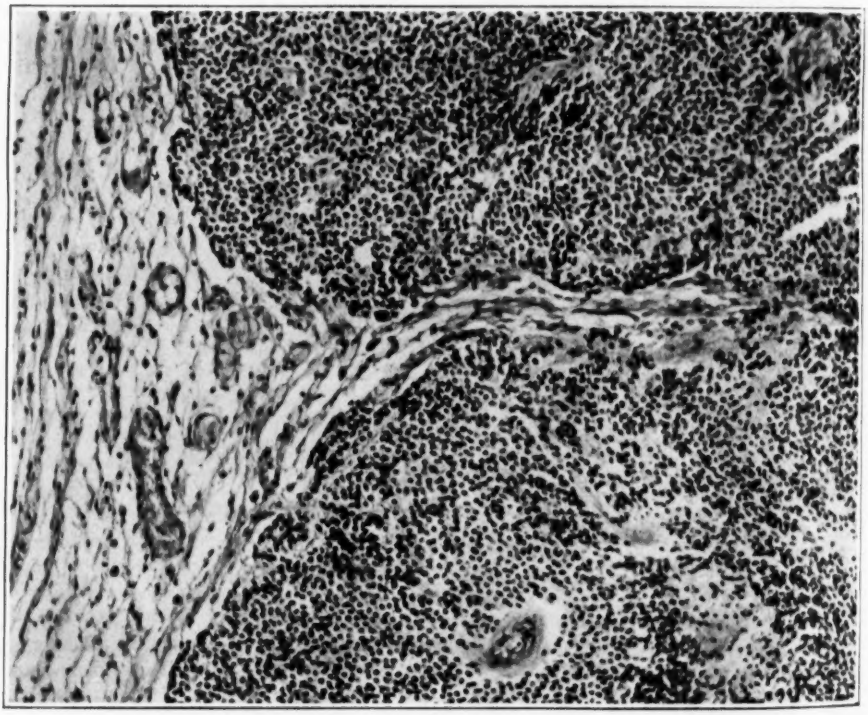

Fig. 33 (case 22).—Section showing the histologic character (sarcomatous) of the tumor. Hematoxylin-eosin stain; × 117.

presented the usual appearance of a fibrous tract in cross section. Often these fibers formed large whorls. In some sections the tumor presented a more cellular appearance, with large cells giving rise to short processes. In other areas aggregations of nuclei were found in the form of nests irregularly distributed among bundles of fibers.

With special stain preparations other features of the tumor structure were disclosed. Thus, Spielmeyer's stain for myelin revealed many bundles of myelinated fibers. The same stain revealed numerous fragments or irregular deposits of a lipoid material. Bielschowsky's silver nitrate stain revealed numerous packed axis-cylinders, many of which were nonmyelinated. It also displayed the character of vascularization of the tumor and the orientation of the vessels in lines parallel to the long axis of the fibrous bundles. With the Globus modification of Hortega's silver carbonate method the character of interstitial cells was well brought out. Their fusiform, bipolar character and their elongated, often kidney-shaped, nuclei were well outlined. Areas of the tumor which gave the impression of a reticular structure in hematoxylin and eosin preparations disclosed numerous glial elements in various stages of differentiation, some of which had acquired the form of mature astrocytes, when studied in silver preparations. In between the fibrous bundles there were well formed astrocytes in variable numbers. Some of these glial elements had exceedingly long processes ramifying in between the fibers. Well formed nerve cells were scattered among the cells. The Van Gieson stain disclosed a few collagenous fibers limited mainly to the adventitial coat of blood vessels and their immediate environment.

Sections of brain taken from the tuberous nodules described under "gross anatomy" as well as from parts of the brain devoid of gross anatomic alterations and remote from the seat of tumor formation revealed changes characteristic of tuberous sclerosis (fig. 32). In such areas there was the general disorganization of the normal lamellar arrangement in the cortex and irregularly distributed nests of either poorly developed or overdeveloped monstrous nerve glia cells found in variable numbers. The poor differentiation of the intracellular structure in the monstrous cells made it difficult to ascertain their glioblastic or neuroblastic character.

Comment.—This tumor arising from the mamillothalamic bundles and presenting the structure of a neurinoma may be grouped with the so-called central neurinomas.[20] But with the realization that in tuberous sclerosis any of the neuroectodermal derivatives may be involved in the developmental disturbances, it becomes conceivable that it is no more than an expression of a focal accentuation of the general process of heterotopia and histiotopia characteristic of tuberous sclerosis.

MENINGIOMA

Striking also is the rarity with which meningioma occurs in children and adolescents. This is somewhat counterbalanced by the greater frequency with which primary sarcoma and sarcomatous meningioma are encountered in the same age groups.

An explanation may be found for this in the modern understanding with regard to the origin and development of such neoplasms. Globus [21] found that previous concepts based on the differentiation of the meningeal cell elements were not satisfactory, for such histogenetic factors are too obscure and unreliable for the development of a satisfactory identification of meningeal tumors. He directed attention to the phylogenetic and ontogenetic processes which take place in the development of the coverings of the brain. He was thus able to show that the mesenchymal (undifferentiated mesodermal) tissue which fills the space between the skin and the neural tube is the source of origin of the several meningeal membranes. The several stages of cleavage and fusion which take place at various times in the lower vertebrates yield finally a vascular layer, the pia, with its extensions into the interior of the brain; an intermediate membrane, the arachnoid; the outermost

20. Globus, J. H.: Neurinome central associé à une sclérose tubéreuse, Rev. neurol. **2**:1, 1933.
21. Globus, J. H.: The Meningiomas, A. Research Nerv. & Ment. Dis., Proc. (1935) **16**: 210, 1937; Arch. Neurol. & Psychiat. **38**:667 (Oct.) 1937.

membrane, the dura, and the periosteum. Since all these layers have a common source of origin, it is easily seen why a tumor may often contain tissues duplicating the structures of all the three membranes and may often contain bone also. Most commonly, such a tumor imitates the structure of the pia by containing vessels variable in dimensions and structure. Not infrequently the growth presents a histologic appearance reminiscent of the mesenchymal tissue (mesenchymatous meningioma) by the lack of cell differentiation and architectural design. From this there is but a short step to the so-called sarcomatous meningioma. Since the type of cell which is most capable of assuming a sarcomatous character is one which is nearest in type to vascular endothelium, a malignant meningeal tumor is likely to be derived from the pia. Because the pia is the meningeal membrane closest to the brain and penetrates its substance along with cerebral blood vessels, it is conceivable that such a tumor may develop within the substance of the brain from embryonal remnants of the pial extensions.

CASE 23.—*Impairment of speech over a period of six months followed by sudden appearance of hemiparesis and signs of increased intracranial tension; craniotomy (right side), tumor, said to be medulloblastoma removed; recurrence of symptoms; second craniotomy, cystic tumor partially removed; decline; admission to the hospital; tumor removed from left parietal region, diagnosed meningioma; temporary improvement; recurrence of symptoms; craniotomy with attempt at removal of tumor, resulting in fatal issue.*

History.—J. F., a boy aged 5½ years, was apparently well until the age of 5 years. It was then noted that his speech was impaired. Six months later his right leg and then his right arm became weak. Shortly thereafter convergence strabismus developed. He began to vomit repeatedly and was taken to a hospital, where a frontoparietal craniotomy (right side) was performed and a large tumor, reported as medulloblastoma, was removed. High voltage roentgen therapy was given. Three weeks after the operation he returned home. Roentgen therapy was continued, but nevertheless signs of recurrence appeared and he was readmitted to the same hospital about two months later (December). A second craniotomy was carried out, with partial removal of a tumor mass and cyst. He left that hospital in January 1936. He continued to receive roentgen therapy. His head grew in size; the right hemiparesis became more pronounced, and headaches and vomiting continued. He entered this hospital for the first time in March 1936.

Examination.—The significant findings included: pale optic disks; a central weakness of the right side of the face; right hemiparesis, and slight ataxia and dysdiadokokinesis on the right side.

Course.—On April 9 he was operated on for the third time and a tumor was removed from the left parietal region. It was reported as a hemangioendotheliomatous meningioma. The patient was discharged in May with a residual right hemiparesis. There was temporary improvement, but in September of the same year headaches in the left temporal region and frequent vomiting returned and the decompression wound became more tense. The child was returned to this hospital on October 3. There were now a slight anomia; a right hemiparetic gait, a more pronounced bilateral papilledema, right homonymous hemianopsia; unequal pupils, the right being larger than the left; central weakness of the right side of the face with a wider right palpebral fissure, and right hemiparesis with a bilateral Babinski sign. Another attempt to remove the recurrent tumor on the fifth hospital day resulted in death of the child during the procedure.

Necropsy of the Brain.—Gross Examination: On removal of the brain, two soft fleshy tumor masses were seen, excrescences approximating each other and arising from the mid-portion of the medial sulcus of each gyrus rectus (fig. 32). There were two or three small arachnoid cysts about the middle of the convexity of the left frontal lobe. The inner surface of the dura lining both posterior fossae showed eight or ten nodules varying from 1 to 3 cm. in their various dimensions and of a consistency similar to that found in the gyri recti. A few small masses, obviously identical in nature with the others, were seen on the dural floor of both posterior and middle fossae (fig. 33 *A*).

Microscopic Examination: The tumors of the frontal lobe were different from those found in the dura. The former showed the structure best described as a round cell sarcoma, although the cells were somewhat larger, contained a larger amount of cytoplasm and had vesicular nuclei. However, the intimate relationship of the tumor to the overlying pia was readily seen (fig. 34).

The tumors in the medulla were more of the nature of leptomeningioma and appeared as islands surrounded by collagenous fibers (fig. 33 *B*).

Comment.—The events preceeding and following the several craniotomies indicate that the tumor was of a malignant variety, belonging to the group of sarcomatous meningiomas. This applies to the lesions in the brain and is seen in the rapid recurrence following each removal of the tumor.

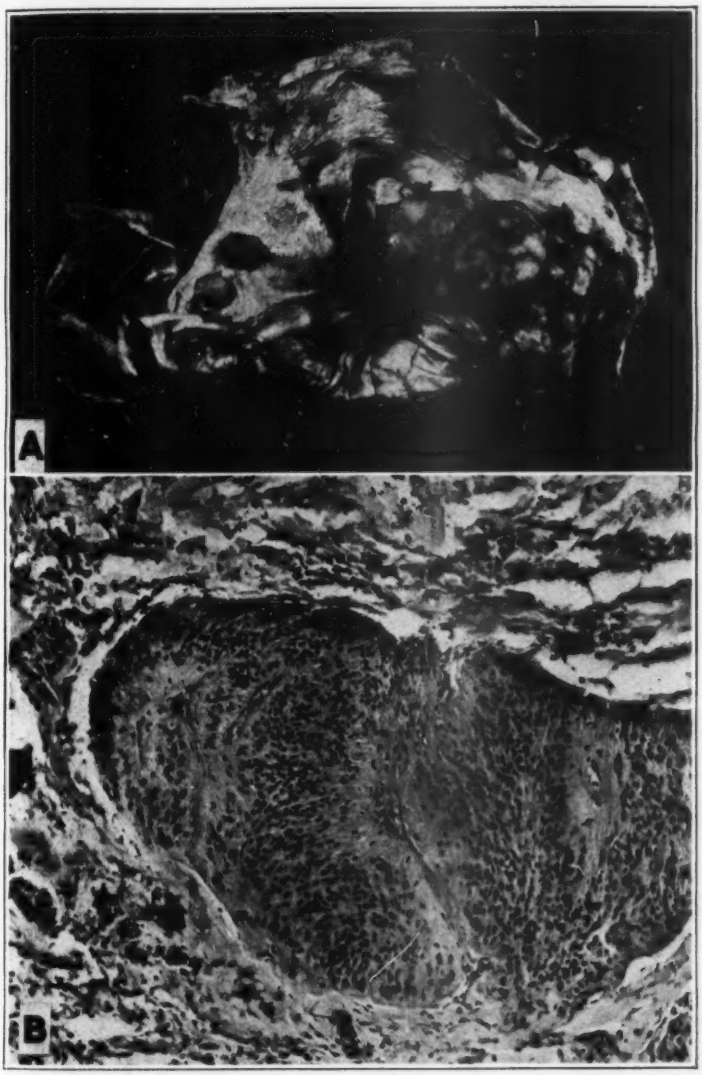

Fig. 34 (case 23).—*A*, dura mater, showing numerous tumor nodules; *B*, section of one of the tumor nodules, exhibiting the structure of a leptomeningioma. Hematoxylin-eosin stain; × 87.

CASE 24.—*Primary sarcoma; convulsive seizure, diagnosed as epilepsy, for two years; history of trauma to the head; headaches, impaired vision followed by papilledema; cerebral neoplasm diagnosed; craniotomy; death; necropsy.*

History.—A. G., a youth, entered the hospital at the age of 17 years (Dec. 17, 1923). As an infant he was subject to convulsions while teething. At the age of 11 years he was struck over the right frontal region by a swing, but he did not lose consciousness and

showed no evidence of injury to the skull. He remained well until the age of 15 years, when he became subject to recurrent convulsive seizures. They were alternately right-sided petit mal attacks and generalized convulsions. As they increased in frequency and severity

Fig. 35 (case 24).—Lateral surface of the hemisphere, showing the tumor in the sylvian fissure.

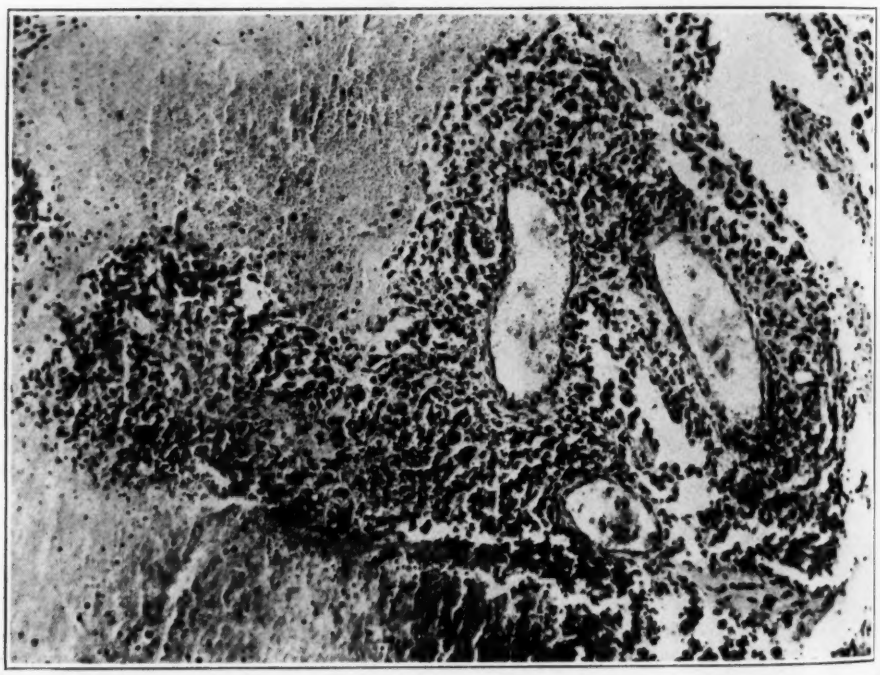

Fig. 36 (case 24).—Histologic appearance of the tumor shown. Hematoxylin-eosin stain; × 190.

the patient became irritable and unstable. The diagnosis of essential epilepsy was made, and the boy was admitted to an institution for epileptic patients. Four months later he began to complain of severe headaches and of rapid impairment of vision. His general strength diminished progressively, and he became bedridden. A tumor of the brain was suspected, and he was transferred to this hospital.

Examination.—Vision was poor; there was bilateral papilledema; the pupils were unequal, the right being larger than the left. There was bilateral ptosis, more marked on the right side. The right external, internal and superior rectus muscles were completely paralyzed. The patient exhibited peripheral facial weakness, hemiparesis and a positive Oppenheim sign on the left. The abdominal reflexes were diminished bilaterally. There were rigidity of the neck and a bilateral Kernig sign.

Course.—An exploratory craniotomy on the left side was done on December 22, but no tumor was disclosed. Three days later complete blindness set in. The patient died one month after operation.

Necropsy of the Brain.—Gross Examination: The brain was removed through the operative wound, and consequently its gross appearance was somewhat disturbed. In the main it showed evidence of increased intracranial tension, such as flattening of the gyri, some dulling of the meninges and a large hard mass situated in the gaping right lateral fissure (fig. 35). The leptomeninges in this area were particularly dull and thick.

Microscopic Examination: Sections of the tumor disclosed large necrotic areas enclosing islands of neoplastic cells (fig. 36). The cells were fairly large, contained a large vesicular nucleus and were surrounded by a fair amount of cytoplasm. The cells were mostly round. They had a tendency to arrange themselves about blood vessels. Here and there a very large cell was found scattered among the smaller cells. The tumor cells could be traced into the leptomeninges, there forming small nodular collections about blood vessels in the pia-arachnoid space.

Comment.—It is interesting to recall that one of us (J. H. G.), having made the clinical observations in the case, because of the meningeal signs diagnosed the lesion as a tuberculoma situated in the sylvian fissure associated with tuberculous meningitis. While he was wrong as to the character of the lesion, he was correct in locating it in the lateral fissure, a common site for tumors of meningeal derivation.

CASE 25.—*Sudden onset of signs pointing to increased intracranial tension; later development of signs of cerebellar dysfunction and meningeal irritation; tumor of brain stem extending to vermis considered; craniotomy; tumor of fourth ventricle found and partially removed; death shortly thereafter; necropsy.*

History.—R. A., a boy aged 11 years, was well until three months before admission to the hospital. He then suddenly began to experience periodic attacks of dizziness followed by vomiting. At the end of two months he seemed to have recovered. He was free of symptoms for about three weeks. During the subsequent week he experienced severe headaches and became dizzy when he attempted to stand. With this he became hypersensitive to light, and pain in the lower part of the back developed.

Examination.—The patient was a poorly nourished boy. His gait was unsteady, with a tendency to stagger, mostly to the right and backward; his head was tilted to the right with the chin carried to the left. There was slight nuchal rigidity, with a bilateral Kernig sign. Early papilledema was present on the left side; the pupils were unequal, the right being larger than the left; both external rectus muscles were paretic; there was a coarse nystagmus in all directions. The patient complained of double vision and was sensitive to light. A slight weakness of the left side of the face, considerable generalized hypotonia and asynergia of the left upper extremity were present. The knee jerks were noticeably depressed and the ankle jerks diminished; there was a bilateral Chaddock sign.

Laboratory Data.—The cerebrospinal fluid was under an initial pressure of 440 mm. of water; it was clear and contained 30 cells per cubic millimeter, mostly polymorphonuclear leukocytes. Wassermann reactions of the blood and of the cerebrospinal fluid were negative. A blood count disclosed 16,000 white cells of which 94 per cent were polymorphonuclear leukocytes.

Course.—A tumor of the brain stem extending to the vermis was diagnosed. Two days after the patient's admission a suboccipital craniotomy was performed. A tumor was found in the fourth ventricle resting on the medulla, beneath the vermis, and extending down into the spinal canal. Part of the tumor was removed. The patient died shortly after the termination of the operation.

Necropsy of the Brain.—Gross Examination: The pons and medulla were greatly swollen. In the right cerebellomedullary angle there was found a brown, cystic mass. On sectioning of the brain, a tumor was seen to extend throughout the entire length of the midbrain, pons and medulla oblongata (fig. 37 *A*). It completely replaced the tegmentum

of the pons, completely filled the overlying ventricle and extended backward into the vermis, involving partially the dentate nucleus. As it entered the midbrain, the tumor assumed the dimensions of the tectum and tegmentum of that structure, here, too, completely filling the aqueduct of Sylvius. When the tumor was traced backward into the medulla on the level of the transition of the pons into the medulla, it was found to have left but a narrow rim, which may have included some of the pontile fibers and possibly a few of the corticospinal fibers. The rest of the tegmentum and adjacent parts were com-

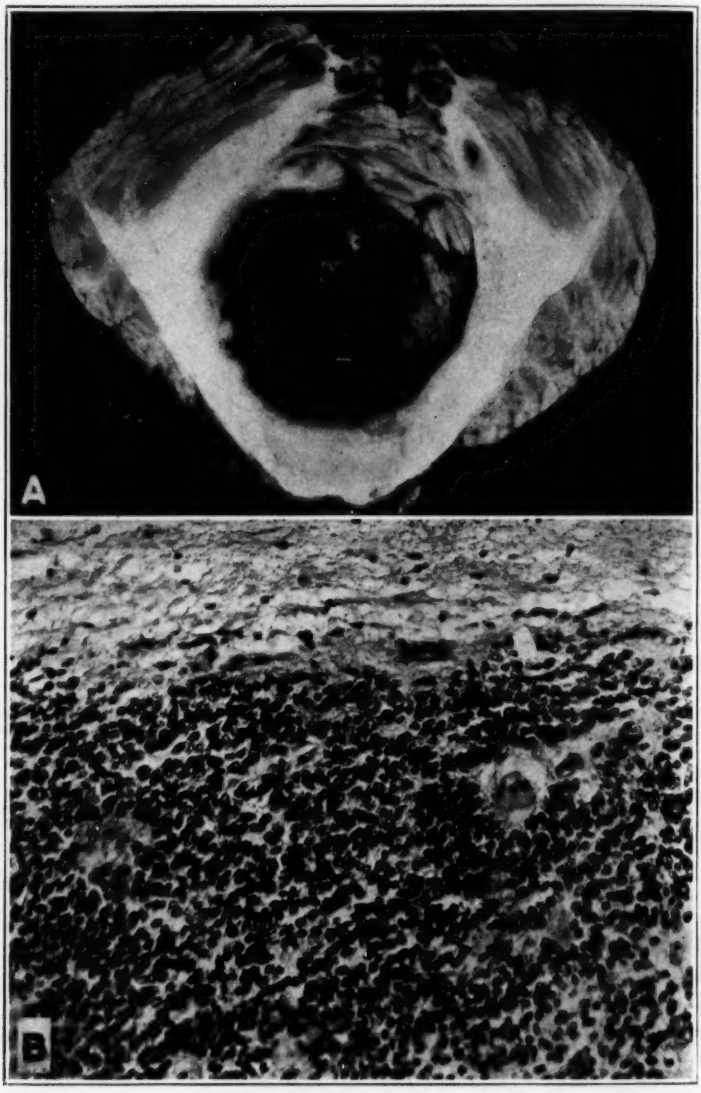

Fig. 37 (case 25).—*A*, coronal section of the cerebellum and pons, exhibiting a large vascular tumor filling the fourth ventricle; *B*, histologic structure of the tumor. Hematoxylin-eosin stain; × 170.

pletely replaced by the tumor. At the level of the nucleus cuneatus the tumor measured about 4 cm. in diameter and was surrounded by an area of softening.

Microscopic Examination: The tumor consisted of numerous vascular sinuses in a cellular structure made up of large cells with round to oval deeply chromatic nuclei. In many places the cells were arranged in layers in a radial formation about the blood vessels. In one section the cells were more loosely arranged in a reticular network. There were numerous areas of necrosis, hemorrhage and hyalination. Very few mitoses were observed.

Comment.—This tumor clinically and grossly could have been considered a medulloblastoma had it not been for the microscopic observations, which showed it to be a sarcomatous meningioma. This question may still be raised: How does such a tumor extend into the brain substance? This was answered in the introductory remarks. Moreover, it is well known that even a so-called benign meningioma may spread along extensions of the pia into the interior of the brain.

GENERAL COMMENT

Anatomic Considerations.—Reference was made in the introductory remarks to the types of tumors prevalent among children and adolescents and to the more common locations favored by the tumors in these age groups. Attention was also drawn to the fact that tumors the origin of which can be best traced to embryonal

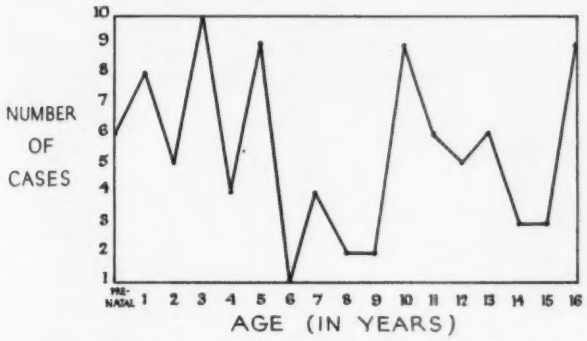

Fig. 38.—Age distribution of tumors (92 cases).

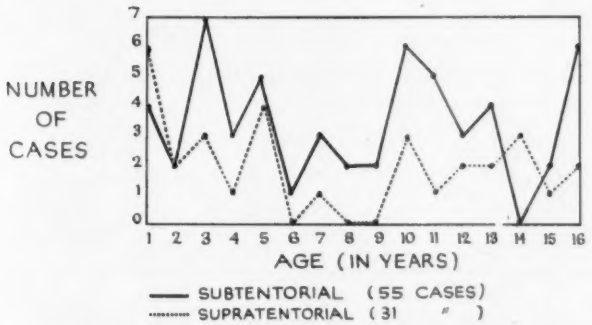

Fig. 39.—Age distribution of tumors (86 cases).

residues, such as craniopharyngioma, pinealoma, infundibuloma, hemangioendothelioma and ependymoma, constitute the largest proportion of neoplasms among children. This obviously is highly significant, as it serves as convincing evidence in support of the Cohnheim embryonal rest theory of formation of neoplasms. This concept finds further support in the occurrence of tumors, particularly such growths as spongioneuroblastoma, in association with a disseminated blastomatous malformation of the brain in the nature of tuberous sclerosis. With the weight of evidence provided by a large number of cases in favor of the embryonal residue concept of formation of tumors, it seems that a similar explanation for the origin of the neoplastic process may be advanced for the remainder of the neoplasms in the entire group.

Age Distribution.—Consideration of the ages of the patients in the cases herein surveyed, presented in the accompanying graphs (figs. 38 and 39), yields some

striking disclosures. Of the 92 patients, 42 were children between the ages of and 5 years (inclusive), while between the ages of 6 and 9 (inclusive) there we only 9, but that from the tenth year and upward to the sixteenth (inclusive) t incidence rose again to 41. Within each of these three subdivisions there a variations from year to year, but what is most striking is the low incidence tumors between the ages of 6 and 10 years. This may be due in part to the fa that autochthonous blastomas (pinealoma, craniopharyngioma, etc.) are mo common during the early years of childhood and that the gliogenous tumors, me ingioma and hemangioma, are more frequent during the later years of childhoo leaving the indicated short gap. Thus, for instance, of 9 patients with medulloblas toma, 6 were children up to the age of 6 years, while 2 were above the age of 1 leaving only 1 in the intermediate years. The same holds true for craniopharyn gioma, pinealoma and ependymoma.

TABLE 3.—*Tumors in Infants* Verified (Thirteen Cases)*

Diagnosis	Sex	Age, Mo.	Papilledema	Hydrocephal
Medulloblastoma	M	24	+	+
Pinealoma	M	19	+	—
Pinealoma	M	24	+	+
Ependymoma	M	2½	—	+
Ependymoma	F	5	+	—
Ependymoma	M	14	—	+
Glioma (subependymal)	M	5	—	+
Spongioneuroblastoma	F	18	+	+
Tuberous sclerosis	M	4	—	+
Tuberous sclerosis	M	5	—	—
Metastatic	M	24	—	—
Metastatic	M	24	—	—
Colloid cyst	M	24	—	—

* Two years old or younger.

TABLE 4.—*Sex Distribution of Patients (Ninety-Two Cases)*

	Male	Female
No operation	11	8
Minor surgical procedure	7	3
Craniotomy	41	22
Total	59	33

Tumors in infants are often said to be exceedingly rare. This is not borne out by our material, which includes 13 cases (table 3) of tumor in infants of 2 years or less. Among the patients were 2 with ependymoma, a 10 week and a 5 month old infant, and 1 with glioma, a 5 month old child. There were 2 with tuberous sclerosis, infants of 4 months and 5 months respectively.

Sex Incidence.—An observation the significance of which awaits explanation is the preponderance of male patients in our group (table 4). There were 59 males and 33 females, almost a 2:1 ratio. When this is further investigated it is found to bear some relation to the fact that the autochthonous type of tumor was found to be more common in the males. Thus, of 9 medulloblastomas, only 1 was in a female; of 9 pinealomas, 2 were in females; of 7 ependymomas, 2 were in females. The reverse is true of some of the spongioblastic varieties; of 9 spongioneuroblastomas, 6 occurred in females.

Clinical Manifestations Briefly Considered.—It has already been mentioned elsewhere that the cardinal signs of an intracranial tumor in an adult are also mani-

ted by intracranial neoplasms in persons of the younger age groups. However, ere is a moderate shift of signs and symptoms in certain directions (table 5). us, vomiting seems to be the earliest and most frequent manifestation; headache next, and papilledema is third in order of greatest frequency. Of significance also the observation that papilledema and headache are often absent in pontile iogenous tumors (of 5 cases, these signs and symptoms were absent in 4). nvulsions are not uncommon in cases of supratentorial tumor but were altogether sent in the cases of infratentorial tumor of our material, except for their occurnce in only 1 case of pinealoma. On the other hand, vegetative dysfunction, such delayed or accelerated development of secondary sex characters, metabolic disrbances, particularly disturbance in water balance, imbalance of temperature gulation, resulting in a temperature-pulse discord, and, finally, manifestations inting to disturbed gastrointestinal functions are more common in the younger age oup. Here, too, the explanation may be found in the type and localization of the mor most commonly encountered in children. The craniopharyngioma, located the interpeduncular space, is in direct contact with the seat of the central vegetave centers in the hypothalamus, while the pinealoma, obstructing the aqueduct, uses secondary hydrocephalus, with the result that the floor of the third ventricle

TABLE 5.—*Primary Tumors in Children (Eighty-Seven Cases)*

General Signs	Cases	Percentage
Vomiting	63	73
Headache *	61	70
Papilledema *	57	66
Hydrocephalus †	16	19
Convulsions ‡	13	15
Atrophy of the optic nerve	3	4

* Of 5 children with pontile glioma, 1 had papilledema and headache; 4 had no papilledema and no headache.
† Visible enlargement of the head was not found in patients with hemangioma of the cerebellum.
‡ Twelve patients with a supratentorial tumor, 1 with a pinealoma.

compromised. Thus, these growths are prone to cause hypothalamic disruption ith consequent vegetative dysfunction.

Trauma as a Factor in the Clinical Course.—In some of the cases a history was btained of violence to the head shortly before the onset of symptoms as discovered y the parents. However, experience with a larger group of tumors in adults,[22] ith the types of tumor and their state and size as disclosed at the end of the clinical ourse, leads to the conclusion that trauma plays no role in initiating or accelerating he growth of the tumor and hence does not influence the clinical course.

Surgical Intervention.—It is quite obvious that with certain types of tumor the atisfactory results of surgical treatment cannot be disputed. This holds true paricularly of cerebellar hemangiomas and of some craniopharyngiomas. Even with few other types of growth (table 6) the results are such as to invite surgical interention. Indeed, in the largest number of cases, because of the character and ocation of the neoplasm operation offers little if any promise for substantially xtending the life span of the patient. But if prolongation of life is thought desirable, o matter how brief the extension, then operation is justified (table 7). However, t is most advisable to obtain a thorough knowledge of the neoplastic process, by iopsy if possible, before a more radical step is undertaken.

22. Globus, J. H.; Zucker, J.; Sapirstein, M., and Kanzer, M.: Brain Tumor and Head Trauma, Tr. Am. Neurol. A. **66**:165, 1940.

High Voltage Roentgen Therapy.—The value of high voltage roentgen therapy and its effects on the clinical course of tumors of the brain in children is still an open question. There are, however, some indications to favor the use of this therapeutic measure (tables 7 and 8). Of our 20 living subjects who were subjected

TABLE 6.—*Postoperative Survival Period of Living Patients (20)*

Diagnosis	Living Patients	Survival Period, Yr.
Hemangioma (10 patients)	1	1
	2	2
	1	3*
	2	4
	1	6
	1	7
	1	15*
	1	16
Craniopharyngioma (3 patients)	1	1*
	1	4*
	1	7
Schwannoma (2 patients)	1	4
	1	5
Cysts (gliogenous) (2 patients)	2	10†
Tuberous sclerosis (2 patients)	2	8†
Spongioneuroblastoma (1 patient)	1	1*

Average survival (20 patients) 5.9+ years; without roentgen therapy (11 patients) 5.5+ years; with roentgen therapy (9 patients) 6.5+ years.
* Roentgen therapy was used with 1 patient.
† Roentgen therapy was used with 2 patients.

TABLE 7.—*Duration of Entire Clinical Course in Fatal (Seventy-One) Cases*

Treatment	Cases	Average in Weeks
No operation	18	36*
Minor surgical measures	10	22
Craniotomy without high voltage roentgen therapy	33	69*
Craniotomy with high voltage roentgen therapy	10	80*

* Fractions not given.

TABLE 8.—*Postoperative Survival Period in Fatal Cases Following First Craniotomy*

	Cases	Average in Weeks
All cases	42	18
Without roentgen therapy	33	9
With roentgen therapy	9	49

TABLE 9.—*Roentgen Treatment*

	Given	Not Given
Hemangioma	3	7
Craniopharyngioma	2	1
Gliogenous cysts	2	0
Schwannoma	0	2
Spongioblastoma	1	0
Tuberous sclerosis	1	1

to craniotomy and removal of tumor tissue, 9 received high voltage roentgen therapy and at the time of writing have shown an average survival period of more than six and one-half years; the remainder, 11 patients, who did not receive roentgen therapy, have shown an average survival period of over five and one-half years.

Since both groups consist of living survivors, the comparison cannot be considered as final. It is equally true that this comparison cannot be regarded as establishing the failure of roentgen therapy to contribute to the length of the postoperative survival period. It is also necessary to bear in mind the differences in the character of the tumors subjected to treatment in this group (table 9).

Of the 43 cases in which there was resort to craniotomy with fatal outcome, 10 of the patients received roentgen therapy over varying periods of time. The average survival period of the treated patients was close to fifty-two weeks, while for the 33 untreated patients it was only nine weeks. In the cases without operation the number of patients who received roentgen therapy was too small to be of any statistical value.

SUMMARY AND CONCLUSIONS

Ninety-two verified cases of tumor of the brain encountered in children and adolescents are surveyed clinically and anatomically.

While on the whole expanding intracranial lesions in persons of these age groups (from infancy to 16 years of age) behave clinically in a way similar to those occurring in older persons, they exhibit some clinical departures which deserve attention.

Among these deviations is the frequent absence of papilledema associated with tumors localized in the pons, a situation which causes severe internal hydrocephalus and hence should be a more common cause of choked disks.

There is also the greater incidence of manifestations of vegetative dysfunction, expressed in retarded or accelerated development of secondary sex characters. These manifestations are of course readily explained by the greater incidence in children of suprasellar tumor (craniopharyngioma), which by direct pressure causes anatomic and hence physiologic disturbance in the tuber cinereum, the seat of the centers controlling vegetative activity. The same holds true for pinealoma, which exercises its influence on the hypothalamus indirectly by blocking the iter and thus causes hydrocephalus, which in turn causes the excessive thinning, stretching and disruption of the floor of the third ventricle, including the tuber cinereum. Indeed, older persons do not altogether escape such an effect, although, as regards sex characters, regression is the more common disturbance in them.

In line with the foregoing manifestations is the occasional symptom of abdominal distress or obstipation, both conditions probably being central in origin.

Another striking feature for which no explanation is yet available is the low incidence of tumors in children between the ages of 6 and 10 years.

As to the types of tumor prevalent in children and adolescents, it seems that the autochthonous blastomatous tumors predominate, an observation which supports the view that cerebral neoplasms in the majority of instances probably originate from embryonal rests. The best examples of such tumors are craniopharyngioma, pinealoma, ependymoma and hemangioendothelioma.

Trauma to the head, although recorded in a few cases as marking the onset of symptoms of intracranial involvement, is found to be of no significance as a precipitating or accelerating cause of growth of the tumor.

Surgical intervention accomplishes much for patients with a tumor of the hemangiomatous group and holds out fair promise for some with craniopharyngioma, but with the latter growth the surgical results are best when they are of a more conservative character.

The value of roentgen therapy cannot be estimated with any degree of accuracy on the basis of the small numbers of cases available for this study in which this treatment was used, but there is evidence that it deserves further trial and study.

900 Park Avenue.

Alton State Hospital.

Abstracts from Current Literature

Hygiene; Growth and Nutrition; Public Health

INFANT MORTALITY IN SANTOS: ITS CAUSES AND WAYS TO OFFSET THEM. CLOVIS LACERDA, Arch. de pediat. **13**:17 (Jan.) 1941.

This is a thorough and comprehensive report on infant mortality in the city of Santos, Brazil, which can be applied to many tropical localities in which the same environmental and climatologic conditions obtain. The ecologic causes have been most exhaustively studied and are considered to be the chief cause of mortality. Social laws and intensive education for the poorer classes, who have here, as in all countries, the highest death rate, are considered the principal weapons.

In brief, the author concludes that, even though infant mortality depends largely on general social conditions, these conditions are enormously intensified by economic and educational problems, which should be attacked by governmental action. SOTO, Habana, Cuba.

WEIGHT OF HEALTHY BREAST-FED INFANTS DURING THE FIRST YEAR OF LIFE. G. V. SYDOW, Acta pædiat. **28**:8, 1940.

The "normal weight curves" which appear in the advertising literature of Swedish manufacturers of scientific instruments are based on Heubner's measurements of children confined in German hospitals. Previous efforts to design standards more appropriate to Scandinavian children are those of Peterson (1880), of Fröhlich (1921), of Höjer (1926), of Schiötz and Berghoff (1928) and of Monrad (1934). Of these none fulfils completely the criteria that the sample be strictly representative of the population which it professes to estimate, that it include only children who are healthy in a carefully defined sense of the word and, finally, that the results of measurement be converted into efficient statistics which define not only the central tendency but the range of variation at successive ages.

Sydow presents data gathered from serial observations on the weight of 1,073 infant clients of the Children's Welfare Centers of Göteborg, Sweden. The data were gathered between 1927 and 1937. The individual infants came under observation not later than the ninetieth day of life and were withdrawn not earlier than the three hundred and first day. The lower middle income class was numerously represented; a smaller fraction was drawn from the working class; a small number of infants came from indigent families, and a comparable number, from professional classes. The infants were mostly breast fed up to the age of 6 to 10 months. Some received supplements of cow's milk; these did not exceed 500 cc. daily. Fish liver oils were added at 1 to 3 months, fruit juices at 2 to 3 months, vegetables at 4 to 5 months and in a few of the centers egg yolk at about the same time. After weaning the diet consisted of milk up to 500 cc., porridge, pudding, meat, fish, rye bread and vegetables, divided into three meals. Pediatric supervision was reasonably close.

The mean birth weights and their probable error were for the boys $3,511 \pm 26$ Gm. and for the girls $3,361 \pm 21$ Gm.; the corresponding medians were 3,548 Gm. and 3,399 Gm. Curves of the body weight during the first year were constructed for eight groups segregated on the basis of sex (two groups) and birth weight (four groups for both sexes). The mean values were computed together with their standard error and the variation around the mean represented by one, two and three times the standard deviation. These data are presented in tables and graphs. Their detailed character prohibits reproduction. For comparison with American norms of weight gain the following quotation must suffice: "In examining the figures obtained one is impressed by the fact that children with a low birth weight increase in weight much more rapidly than the larger children. The boys having a birth weight of 2510-3000 gms. had increased twice in weight at the age 98 days and 3 times at the age of 240 days, whereas for the boys in the 4010-4500 gms. birth weight class the average weight was not doubled until the age of 185 days and at one year of age it was hardly 2½ times the value at birth. The maxim that the weight at birth should be twice as high as 6 months of age and three times as high at the age of 1 year does not hold good for any category in this material. The most striking feature, however, is the great range of variation in all the groups examined." MCCUNE, New York.

INFANT MORTALITY AND PREMATURITY. C.-E. RÄIHÄ, Acta pædiat. **28**:27, 1940.

From about 1870 onward the death rate of infants in Finland fell rapidly, reaching 7 per cent between 1931 and 1934. Here it has remained, being 6.59, 6.86 and 6.78 in 1936, 1937 and 1938, respectively. The way toward further reduction is implicit in the facts that a 2 per cent neonatal mortality has remained virtually unchanged for many years and that the 2 per cent incidence of stillbirths has also shown little improvement. All investigators are in agreement that the phenomena are to a large extent causally dependent on prematurity. Räihä's survey of the annual reports of the Helsingfors Women's Clinic for the years 1927 to 1937 verify this opinion. He finds that (1) over half of the stillbirths occur before term and that (2) neonatal deaths predominantly involve premature infants. Since two thirds of the 7 per cent death rate during the first year is due to prematurity, little can be done further to reduce the infant death rate except by lowering the frequency of premature birth and by procuring the survival of premature infants through radical improvement of care.

The investigations of Ylppö's school, the most recent of which have been carried out by Räihä, have shown that the premature infant lives in a state of actual or potential oxygen want. This is due in large degree to the underdeveloped state of the capillary bed. It results in restriction of aerobic combustion and causes metabolism to take place through anaerobic fermentative processes, which lead to the accumulation of excessive amounts of organic acids, chiefly lactic acid. This explanation accounts for the low metabolic rate, the low and rapidly fluctuating values of the respiratory quotient and the reduction of the carbon dioxide content and p_H of the blood, which are characteristic of the premature infant. Oxygen deficit is often exaggerated by anemia. The phenomenon is judged to be responsible for the attacks of cyanosis, the episodes of exhaustion and the low resistance to infection exhibited by premature infants. Räihä recommends the use of an atmosphere enriched in oxygen. He calls attention to a thermostatically controlled, air-conditioned apparatus which he has devised for this purpose. Previously unpublished data on gas metabolism are given.

McCUNE, New York.

Prematurity and Congenital Deformities

THE GROWTH OF PREMATURELY BORN CHILDREN OF SCHOOL AGE. T. BRANDER, Nord. med. (Finska läk.-sällsk. handl.) **9**:212 (Jan. 18) 1941.

Brander reports on the physical development of 370 premature children at 7 to 15 years of age. The average values for length and weight were found to be below normal, and there was no tendency for this difference to diminish toward the end of school age.

WALLGREN, Göteborg, Sweden.

Newborn

COSTAL OSTEOMYELITIS WITH PNEUMOTHORAX IN A NEWBORN INFANT. LESNÉ and RONGET, Bull. Soc. pédiat. de Paris **37**:578, 1940.

This patient, an infant of 1 month, was hospitalized for intense dyspnea developing suddenly a few hours before. Examination showed a well developed nursling, weighing 3.6 Kg., extremely dyspneic and cyanosed; both mammary glands were swollen and inflamed, especially the left, which bore traces of two incisions performed three weeks earlier. There were evidences on this side of osteomyelitis of the rib below the breast, and about the involved area there existed a zone of subcutaneous emphysema. Dulness was made out at the base of the left lung, surmounted by exaggerated tympany. Auscultation revealed the absence of respiratory sounds and the characteristic metallic tinkle of pneumothorax. The infant died before roentgenograms could be secured, but exploratory puncture withdrew air under sufficient pressure to force back the piston of the syringe. Culture of the subcutaneous abscess showed Staphylococcus aureus unassociated with other bacteria. There was an abscess of the left mammary gland. Autopsy showed osteitis of the fourth rib with erosion and a purulent fistula from the posterior side directly into the pleura. The lung was retracted by pneumothorax and covered with a purulent exudate. The age of the patient and the site of attack are declared to be among the exceptional features in this case.

AMESSE, Denver.

PREVENTION OF HEMORRHAGIC DISEASE OF THE NEWBORN BY THE ADMINISTRATION OF COW'S MILK DURING THE FIRST TWO DAYS OF LIFE. L. SALOMONSEN, Acta pædiat. **28**:1, 1940.

Previous observations made by Salomonsen during the month of August have shown that the administration of small amounts of cow's milk during the first four days of the infant's

life obviates almost completely the so-called physiologic hypoprothrombinemia of the neonatal period. In view of the subsequent demonstration of seasonal variability in the clotting time of the newly born infants—the shortest clotting times occurring in the summer—it appeared appropriate to repeat the investigations of the effect of cow's milk at a season when the time required for clotting might be expected to be longest. Accordingly, during the months of January and February two groups of infants were studied. The members of group A, 15 in number, received only breast milk during the first eight days of life. The mean values for capillary clotting time on the successive days from the first to the eighth, inclusive, were: 3.2, 3.9, 4.4, 4.3, 3.7, 3.7, 3.4 and 3.2 minutes. Beginning two hours after birth the 13 members of group B received cow's milk for four days in amounts of from 30 to 120 cc. daily. Their mean capillary clotting times from the day of birth to the eighth day of life, inclusive, were: 2.7, 3.2, 3.0, 2.7, 2.8, 2.7, 2.6 and 2.6. The reliability of the differences between the two groups was supported by comparable discrepancy in the values for the prothrombin time of venous blood. On the third and fourth days of life this was conspicuously prolonged in the untreated group. Attention is drawn to the fact that although cow's milk shortened the clotting times it did not lower them to normal as it had done in the summer study. This finding is interpreted as pointing to hidden variables of a seasonal character in the pathogenesis of hypoprothrombinemia neonatorum. Confirmation of the practical significance of the dietary factor is drawn from the fact that during a six month period there was not a single case of hemorrhagic disease among 1,005 infants who received cow's milk supplements. During the preceding five years there were 40 cases among 4,783 newly born infants who got only breast milk (0.84 per cent). McCUNE, New York.

SOME PROBLEMS OF THE NEWLY BORN: PRELIMINARY REPORT. C. E. RÄIHÄ, Acta pædiat. **28**:391, 1940.

Aside from congenital anomalies of development, the viability of the newly born infant is threatened most seriously by intracranial hemorrhage and by a tendency to acidosis. The latter manifests itself so consistently that unless it assumes grave proportions it may be termed physiologic. Räihä's own observations have shown that in premature infants it is due to restriction of aerobic metabolism in consequence of imperfect development of the capillary bed of the tissues.

The present paper sets forth in a rather desultory way the present status of studies which Ylppö's group is making of the foregoing problems, particularly as they are exemplified in prematurely born infants. Autopsy of 20 premature infants has shown a 59 per cent incidence of intracranial hemorrhage; this agrees with Ylppö's previously published figure of 60 per cent. Demonstration of a correlation between the time at which edema is prone to occur in premature infants and the point at which hemoconcentration is most marked suggests the inference that the phenomenon is due to a shift of water from the vascular to the interstitial compartment. In neither the premature nor the full term infant is the early acidosis accompanied by increased concentration of organic acids in the blood. A modal concentration of 5 milliequivalents per liter appears to prevail; there is considerable variation. Cursory examination of the urine does not reveal a significant increase of organic acids in this fluid. However, more exact studies show that the twenty-four hour excretion of lactic and pyruvic acids is higher than would be expected. This lends support to the hypothesis of fermentative rather than oxidative transfer of energy by the newborn infant.

The several phenomena which point to deficiency of oxygen on the part of newly born premature and full term infants suggests the need for measures designed to overcome the deficiency. Räihä has accomplished resuscitation in apparently fatal asphyxia by intravenous injection of 1 cc. of a 1 per cent solution of methylthionine chloride (methylene blue). An atmosphere of high oxygen content is often critically necessary.

Neonatal hyperbilirubinemia is a result of inadequate flow of blood through the liver. This has been shown to be true in premature infants. Patency of the ductus venosus may be responsible for some cases of physiologic jaundice. A comparable patency produced experimentally in a dog yielded delayed disappearance from the blood of bilirubin injected by vein.

McCUNE, New York.

Acute Contagious Diseases

CEREBROSPINAL MENINGITIS OF NURSLINGS CURED BY EXCLUSIVE USE OF SULFANILAMIDE. M. H. ESCHBACH, Bull. Soc. pédiat. de Paris **37**:549, 1940.

The first case was that of an infant of 4 months suddenly stricken at night with a strident cry, asphyxia and vomiting. These crises were repeated on the following morning and con-

ulsions appeared, involving especially the left side. The temperature rose to 41 C. (105.8 F.). Rigidity of the neck and trunk followed. Intraspinal injection of 10 cc. of a solution of ulfanilamide (concentration not stated) was employed; on the second day the spinal fluid howed 7,500 polymorphonuclear cells but bacteria were not demonstrated. On the third day he baby was apyretic and the symptoms gradually subsided, until within another twenty-our hours the patient was definitely on the way to recovery. A second injection completed he therapeutic management.

In the second case, the author reports the use of this agent in a case of cerebrospinal neningitis in an infant of 6 months. Recovery followed in five days. AMESSE, Denver.

CHEMOTHERAPY OF MENINGOCOCCIC CEREBROSPINAL MENINGITIS. C. GERNEZ and C. HURIEZ, Presse méd. **49**:25 (Jan. 8-11) 1941.

The authors report a series of 20 cases, all with recovery. Four patients received initial erum therapy, with moderate doses of a sulfonamide compound; 4 others received massive loses of a sulfonamide compound with secondary monovalent serum, and 8 received massive loses of a sulfonamide compound with no serum. The first group underwent a longer course, with 3 relapses occurring. One patient acquired septicemia followed by purulent arthritis. Four of this group had serum reactions. In the second group, convalescence was shorter, ut fever and persistence of organisms in the spinal fluid were not overcome until serum as given. The third group received larger amounts of the drug and were cured clinically nd bacteriologically within a week.

The products used were sulfapyridine and sulfanilamide. These were given by mouth, ubcutaneously, intravenously and intrathecally. A concentration of the drug in the spinal luid as high as 5.5 mg. per hundred cubic centimeters was obtained in only 1 patient in he first group. With larger doses, the second group showed values of 7.2 to 8.5, and in the hird group values ranged from 8 to 12.2.

The sulfonamide compounds are eliminated in two forms in the urine. The ratio of the ree to the combined compound should be 2 or 4. Reduction of this ratio indicates an mpending reaction to the drug, and immediate treatment should be initiated.

The authors conclude that successful treatment consists of early administration of large loses of a sulfonamide compound, 1.5 Gm. per kilogram of sulfanilamide and 1 Gm. per ilogram of sulfapyridine, and continuation of the medication for three days after the spinal luid becomes sterile. In cases of resistance to sulfonamide compounds, serum should be given econdarily.

DAFFINEE, Boston.

INTUBATION AND TRACHEOTOMY FOR DIPHTHERITIC CROUP. ESPIDITO DI LAURO, Pediatria **49**:51 (Jan.) 1941.

The author urges the younger laryngologists to make themselves proficient in intubation nd tracheotomy. He believes that the care of diphtheritic croup should be in the hands of aryngologists.

MARTOCCIO, Utica, N. Y.

ERYSIPELAS AND THERAPY WITH SULFONAMIDE COMPOUNDS. ELIEZER AUDIFACE and CARLOS ABREU, Pediat. e puericultura **9**:56 (March) 1940.

After a brief résumé of erysipelas, its complications and gravity, the authors discuss the herapeusis of the disease, concluding that the introduction of the sulfonamide compounds has rought about a great change in the prognosis of this malady, which hitherto showed a mor-ality as high as 80 and even 90 per cent.

After reviewing various foreign statistics on treatments with sulfonamide compounds, they resent case records of 10 children in whom complete recovery was effected within twenty-our to forty-eight hours without untoward effects or symptoms of intolerance. The ages of he patients averaged 13 months and ranged from 26 days to 4 years.

SOTO, Habana, Cuba.

POSSIBILITIES OF ACTIVE IMMUNIZATION AND OF SPECIFIC THERAPY IN DIPHTHERIA. ZOLTAN TEVELI, Arch. f. Kinderh. **119**:44 (Feb. 6) 1940.

The author's experiments on guinea pigs as well as statistics from many countries demon-strate that active immunization against diphtheria is possible. The content of antitoxin of the blood parallels the immunity against diphtheria in the majority of persons. For attaining immunity some people require a larger amount of antitoxin than the average person. Diphtheria

antitoxin (serum) is effective even in cases of diphtheria gravis when applied in the early stage of the disease. In all cases of tonsillitis a bacteriologic examination is recommended in order that the diagnosis of diphtheria may be made as early as possible.

ARON, Chicago.

DR. J. N. HELL, A PHYSICIAN OF SOPRON, INTRODUCES SMALLPOX VACCINATION INTO HUNGARY. LASZLO THIER, Ödenburger Zeitung, Jan. 22, 1939.

The author discusses Jenner's discovery and the role played by Dr. Hell in introducing vaccination in Sopron in 1799 (after Gyula Szilvasi and Andras Csatkai).

[MITT. Z. GESCH. D. MED. U. NATURWISS.]

BLOOD SEDIMENTATION TESTS IN SCARLET FEVER. ALLAN BORBERG, Nord. med. **9**:194 (Jan. 18) 1941.

Three hundred patients with scarlet fever were examined at an interval of one week. In uncomplicated scarlet fever the initial high sedimentation rate slowly decreases until normal values are reached in four to five weeks. In some cases a transitory new elevation of the sedimentation rate occurred in the third week without any clinically demonstrable cause. In complicated cases the sedimentation rate remained high, its value depending on the malignity of the complicating illness. Sometimes the sedimentation increased before the complication was clinically noticeable.

WALLGREN, Göteborg, Sweden.

FATAL CASE OF ENCEPHALITIS FOLLOWING VARICELLA. BERTIL SÖDERLING, Svenska läk.-tidning. **38**:210 (Jan. 24) 1941.

A girl of 6 years, who two years previously had suffered from encephalitis in connection with epidemic parotitis, fell ill with encephalitic signs and symptoms on the seventh day after varicella and died six days later. At the postmortem examination encephalitic changes were found in the pons, in the corpus striatum and in the medulla oblongata.

WALLGREN, Göteborg, Sweden.

Acute Infectious Diseases

SEPTICEMIA AND MENINGITIS OF STAPHYLOCOCCIC ORIGIN. GRENET, GAUTHERON and SAULNIER, Bull. Soc. pédiat. de Paris **37**:574, 1940.

A boy of 4 years was admitted to the hospital Feb. 24, 1940, with a history of fever (the temperature reaching 104 F.) and digestive disturbances for the preceding two days. The patient was a sturdy child with an excellent family and personal history. He had had bronchopneumonia, otitis media, convulsions and measles but was in excellent health at the time of onset of the present illness. On examination he was found in collapse and incoherent and showed the usual signs of beginning meningeal involvement. The spinal fluid, however, at this time was normal. A nonsuppurative hematoma was discovered in the nasal septum, which embarrassed the respiration. Slight dulness below the right clavicle together with the high temperature led the clinicians to suspect pneumonia, but roentgenograms of this area showed no indications of it. On the fifth day, with a much graver picture in general, the hematoma was found to be suppurating and was incised; at the same time a culture of the blood revealed infection with Staphylococcus aureus. On March 3, meningitis developed; but spinal fluid was turbid and contained many polymorphonuclear cells but no bacteria. There were marked edema of the left upper eyelid and distinct exophthalmos, with papillary edema and other evidences of thrombophlebitis of the sinuses. Sulfanilamide, which had been administered from the earliest stage, was continued. Transfusions were given two or three times a week up to March 16. On March 7 there was distinct amelioration, and the meningeal syndrome had disappeared, but on March 19 there was relapse with aggravation of all symptoms; the spinal fluid was found to contain staphylococci (Staph. aureus) in great numbers. The boy continued to do badly, and death came on April 15.

AMESSE, Denver.

ACUTE GONOCOCCIC PERITONITIS IN A GIRL OF NINE AND ONE-HALF. WEILL-HALLE, PAPAIOANNOU and LAGROUA, Bull. Soc. pédiat. de Paris **37**:511, 1940.

This patient was demonstrated at the March (1940) session of the Pediatric Society of Paris. The child had been evacuated from a country district one month before; for the pre-

eding three days there had been an extremely abundant vaginal discharge followed by violent ain in the lower portion of the abdomen. There was moderate fever. On admission to the ospital she presented the usual picture of acute peritonitis. Examination of the vaginal dis-harge revealed numerous gonococci. Sulfapyridine was prescribed in 2.5 Gm. doses, and ice acks were applied locally. The results were immediate and gratifying; within five days a complete cure was effected.

AMESSE, Denver.

STAPHYLOCOCCIC SEPTICEMIA OF RHEUMATIC TYPE. H. GRENET, R. LEVENT and P. ISAAC-GEORGES, Bull. Soc. pédiat. de Paris **37**:571, 1940.

A well developed boy of 13 was admitted to the hospital on Nov. 1, 1938, with a diagnosis of Bouillaud's disease. The patient was pale, perspired profusely and complained of severe pain in the right knee, which was swollen but of normal color. Examination of the heart revealed prolongation of the first sound at the apex, without actual murmur; the blood pressure was 140 systolic and 85 diastolic, and the temperature was 39.8 C. (103.6 F.). The history showed the patient had been taken ill eight days before admission, with severe pain in various joints, especially the small joints of the hands and feet. There were no preceding evidences of angina or of cutaneous infection. Administration of sodium salicylate in large doses was begun immediately, but no relief was obtained. Culture of the blood showed Staphylococcus aureus. The following day purpuric spots appeared on the hands and feet and a frank systolic murmur was heard. The boy continued to do badly and died on November 5.

AMESSE, Denver.

TYPHOID IN INFANTS OF 15 AND 18 MONTHS. MLLE. ABRICOSSOFF, Bull. Soc. pédiat. de Paris **37**:581, 1940.

From the service of Armand-Delille, Abricossoff presents several cases of typhoid in young subjects. The first case is that of a girl of 15 months admitted to the hospital on account of digestive disturbances. The infant was pale and prostrated, was slightly dyspneic because of the elevated temperature, of 40.5 C. (104.9 F.), and had passed numerous greenish yellow stools. Her appetite was completely lost. Cutaneous reactions were negative; the chest was normal on roentgen examination. This typhoid state continued for ten days. The blood picture showed 8,200 white cells, of which 75 per cent were polymorphonuclears. Since the leukocyte count was too high for leukopenia, the diagnosis remained in doubt until rose spots suddenly appeared on the abdomen, the spleen became greatly enlarged and the tongue assumed the characteristic dry appearance. The agglutination reaction was found positive in a dilution of 1 to 200. The patient recovered in the third week; the source of infection could not be determined.

The second case reported is that of an infant of 18 months. The patient had suffered a series of digestive upsets, with anorexia, diarrhea, fever, malaise, insomnia and severe frontal headache. Examination showed an obviously very ill baby struggling against clinical investigation and with marked photophobia. There was profuse diarrhea, and palpation of the right iliac fossa produced a gurgling sound. Meningitis was ruled out; the ear drums were normal; the temperature remained elevated for ten days, when a number of rose spots were noted on the lower part of the abdomen, the spleen became palpable and the agglutination test for typhoid gave a positive reaction. Convalescence was uninterrupted. The epidemiologic study revealed that the baby had eaten freely of oysters fifteen days before the onset of the illness.

Antityphoid vaccination should be employed earlier in life than is now the custom.

AMESSE, Denver.

TYPHOID AND PARATYPHOID IN NURSLINGS. GRENET, GAUTHERON, AUPINEL and SAULNIER, Bull. Soc. pédiat. de Paris **37**:592, 1940.

These infections are so rare in the very young, or at least so infrequently recognized, that they should be kept in mind. The writers report in considerable detail 5 observations on infants varying in age from 7 to 22 months. In 4 of the cases, there was infection with paratyphoid B organisms and in 1 with Eberth's bacillus. Four patients recovered and 1 died, the latter a baby of 7 months with complicating mastoiditis. For those who survived, the period of hospitalization averaged thirty-two days; in the fatal case the child died on the thirtieth day. The source of infection lay in the milk supply, which could not be protected properly under war conditions.

AMESSE, Denver.

PARROT'S DISEASE WITH ICTERUS AND UMBILICAL HEMORRHAGE. HALLEZ and GARNIER, Bull. Soc. pédiat. de Paris **37**:624, 1940.

Parrot's disease has a maximum frequency between birth and the end of the third month, when it becomes an ossifying periostitis. A case with precocious evolution is reported by these clinicians. The infant was born spontaneously at eight months, weighing 3,050 Gm. The placenta weighed 860 Gm. and had the characteristic appearance found in syphilis. There was persistent cyanosis, and the abdomen was voluminous, partly because of the greatly enlarged liver. The spleen was barely palpable; the skin was wrinkled and covered with soft hair; the right hand was deformed. On the third day icterus was noted, and on the fifth there was swelling of the left arm extending to the elbow. The skin of this region was reddened and edematous. Movement of the arm was painful. Roentgen examination revealed osteochondritis of the inferior epiphysis of the left humerus. The roentgenograms of the skeleton showed other portions involved, including the distal extremity of the radius and left cubitus. On the ninth day there was hemorrhage from the umbilicus, which was repeated through several days in spite of the injection of maternal blood and the use of calcium chloride and local coagulants. The infant died on the eleventh day, although intensive syphilitic treatment had been employed since birth.

AMESSE, Denver.

THE SO-CALLED PLAGUE OF THUCYDIDES: INTERPRETATION AND IDENTIFICATION. BENNO VON HAGEN, Jahrb. d. Akad. Gemeinnütz. Wissensch. zu Erfurt N. F. **64**:159, 1939.

The author, a philologist, assumes with Veil of Jena that at the time of the plague Athens was suffering simultaneously from two epidemics, one of smallpox and one of typhus.

[MITT. Z. GESCH. D. MED. U. NATURWISS.]

CASE OF TULAREMIA CAUSED BY INSECT BITE. T. TJÖTTA, Nord. med. (Norsk mag. i. lægevidensk.) **9**:285 (Jan. 25) 1941.

Tjötta reports a case of tularemia probably caused by bites of mosquitoes. The primary lesion was localized on the very spots where the patient was bitten by the insects, and he had had nothing to do with any kind of rodent.

WALLGREN, Göteborg, Sweden.

Chronic Infectious Diseases

POTT'S DISEASE AND SUDDEN DEATH IN A CHILD OF FOUR. JOSEPH LOUINEAU, Bull. Soc. pédiat. de Paris **37**:516, 1940.

Infection in this boy first appeared as a painful inguinal lymph node. The gland was as large as a prune pit, movable under the skin and sensitive on pressure. Various local applications were ineffective. Two months later the patient complained of severe pain in the abdomen and was unable to walk; the cutaneous reaction to tuberculin was strongly positive, but roentgenograms of the hips and spine showed no evidence of tuberculosis. Tuberculous peritonitis was considered. After a few weeks meningeal signs were noted, with rigidity of the neck, a positive Kernig sign, projectile vomiting, photophobia and a noticeable change in disposition. A diagnosis of tuberculous meningitis was declared, although the spinal fluid was normal in all respects. Roentgen examination of the spine now revealed severe involvement of the sixth and seventh dorsal vertebrae. A suitable corset was fitted, and the child was sent to a seaside sanatorium. One month later, after conversing with his father he suddenly sat up in bed, a thing he had not been able to accomplish for many weeks, extended both arms and fell back dead.

The discussion of this case brought out the impression that sudden death is common in Pott's disease of the clavicular region, while with Pott's disease in the dorsolumbar area it is extremely rare.

AMESSE, Denver.

SCROFULOSIS IN CHILDHOOD: HISTORICAL REVIEW FROM HIPPOCRATES TO THE PRESENT TIME. ILSE GRIMM, Dissertation 190, Düsseldorf, Germany.

The author presents at first the etymology and historical explanations of the word scrofulosis and then the old opinions on the connection between scrofulosis and phthysis; he cites extensive remarks on this subject by Charmetton, Baumes and Hufeland, as presented by these men in "French Prize Essays of 1786." He continues with further development in the

knowledge of the disease, the ideas held in the pathologic-anatomic era and material dealing with the experimental and bacteriologic examinations of the contents of scrofulous glands, and finally presents modern ideas on the problem.

[Mitt. z. Gesch. d. Med. u. Naturwiss.]

THE STATE OF ALLERGY EXHIBITED BY TUBERCULOUS CHILDREN IN GOTHENBURG, WITH PARTICULAR REFERENCE TO GRÖER'S ALLERGOMETRIC METHOD. E. KOENIGSBERGER, Acta pædiat. **28**:44, 1940.

The results of tests of sensitivity to tuberculin carried out on 18 children with active tuberculosis failed, on the whole, to confirm the observation of Gröer that several types of this infection exhibit a characteristic sort of allergy. The results on 6 children who had previously been inoculated with BCG showed good agreement with Gröer's. However, the number of tests was too small to permit their being accepted as conclusive confirmation of Gröer's contention, particularly since other investigators have obtained conflicting results in larger series. Two possible causes of discrepancy are discussed: first, inaccuracies of technic; second, the high reactivity to tuberculin which is known to characterize infected Scandinavian children.

McCUNE, New York.

INTERVAL BETWEEN RENAL TUBERCULOSIS AND INITIAL TUBERCULOSIS. HANS JACOB USTVEDT and JOHAN WEIDMANN, Tidskr. f. d. norsk. lægeforening. **61**:74 (Jan. 15) 1941.

In 57 cases of renal tuberculosis the disease manifested itself within the first year after the initial tuberculosis (erythema nodosum or pleurisy) in only 5 cases and within the first five years in only 18 cases. In 17 cases the interval amounted to more than fifteen years.

WALLGREN, Göteborg, Sweden.

Diseases of Blood, Heart and Blood Vessels and Spleen

THE HEART AND VASCULAR SYSTEM DURING PUBERTY. N. I. OSSINOWSKY, Acta pædiat. **28**:56, 1940.

Palpitation, precordial discomfort, breathlessness, excessive sweating of the extremities and acrocyanosis are common phenomena during puberty. A survey of their occurrence, singly or combined, in a group of 273 Russian children revealed their presence in 25 per cent. Comprehensive examination of the affected subjects failed to reveal demonstrable disease of the organs of circulation. The symptoms are ascribed to endocrine causes.

McCUNE, New York.

CASE OF TRAUMATIC RUPTURE OF THE HEART VALVES. N. AHLBERG, Acta pædiat. **28**:69, 1940.

Warburg's recent monograph draws attention to the fact that injury to the pericardium and to the heart muscle itself through concussion is not so uncommon as it used to be thought to be. Injury to the valves through nonpenetrating violence is still regarded as rare. The first case was reported on by Senac in 1778. The number of verified instances remains small.

The author describes the misfortune of an 8 year old boy who was struck forcibly by a supporting post when the hammock in which he was lying collapsed. Dyspnea, hemoptysis and abdominal pain were immediate. Two hours later the boy was ashen and continued to bring up blood-tinged sputum. The chest and the abdomen were bruised in the midline; the ribs were intact. The heart was not enlarged; its rate was 160 and its rhythm regular. There was a long, whistling systolic murmur, loudest in the sixth intercostal space just to the left of the sternum. The systolic blood pressure was 110 and the diastolic pressure 80 mm. of mercury. There was dulness over the left lung and a bronchial quality to the breath sounds at the base of this lung. The abdomen presented nothing unusual. On the following day all pathologic physical features were less marked. Roentgen examination showed rupture of the diaphragm with herniation of the intestine into the chest. During four months' observation the boy showed slight dyspnea on exertion, gradual enlargement of the heart and transient slight changes of the T waves in the electrocardiogram. To the systolic murmur there was added a diastolic adventitious sound which was demonstrable only by the phonocardiogram. Two years after the injury the child was well and active.

A useful bibliography is appended.

McCUNE, New York.

Diseases of Nose, Throat and Ear

TRACHEOCELE: REPORT OF A CASE. GRENET, GAUTHERON and SAULNIER, Bull. Soc. pédiat. de Paris **37**:507, 1940.

The authors report a case of tracheocele in a boy of 3½ years, first seen five months before, when he was brought for relief of a soft tumor occupying the subclavicular spaces. This swelling appeared suddenly in the course of a violent fit of coughing, as noted by the mother. Examination showed a tumor as large as a medium-sized orange, soft, painless and sonorous on percussion. There was no crepitation, and its volume was augmented by effort; reduction could not be effected.

Aside from this, the child was entirely well. Several punctures were made, and air was withdrawn on each occasion together with a small quantity of a clear fluid in which a few red cells were found. The fluid was sterile, and laryngoscopic and roentgen examinations revealed no abnormalities. Injection of the tumor with iodized poppyseed oil showed that the cavity extended from the tracheal region a little below the larynx, but it was not possible to demonstrate a communication. This condition must be differentiated from pneumocele, which is crepitant and is always accompanied by functional disturbances, and from subcutaneous emphysema in which crepitation is also found and in which the causative agent is usually readily apparent.

The tracheocele under discussion was doubtless due to congenital weakness of certain muscle fibers.

AMESSE, Denver.

SYPHILITIC MEDIASTINITIS IN AN INFANT OF TWO MONTHS. WEILL-HALLE and PAPAIOANNOU, Bull. Soc. pédiat. de Paris **37**:510, 1940.

This infant was born at term, weighed 2,990 Gm. and was the third child in the family. After a loss of 300 Gm. during the first three days, it gained regularly. At 3 weeks, the reporters examined the baby and found it apparently normal with the exception of a slight pallor and bilateral hydrocele; the liver, the spleen and the epitrochlear glands were not palpable. In the fifth week retraction in both the episternal and the substernal area was noted, with obvious embarrassment of respiration. A pulmonary roentgenogram showed a quadrangular shadow almost covering that of the heart; the reaction to tuberculin was negative, and cough was absent.

The diagnosis at this time was obscure; an enlarged thymus was considered, but the shadow was much lower than usual and of a different shape. Although the Wassermann reaction of the mother was positive, that of the patient was negative. In the belief that syphilitic mediastinitis was present, mercurial inunctions were employed, followed by injections of sulfarsphenamine, but the latter provoked vomiting, and the inunctions were resumed. The patient was still under treatment at the time the case was reported.

AMESSE, Denver.

ASTHMA REFLEX ORIGINATING IN THE TONSIL. F. CHAVANNE, Oto-rhino-laryng. internat. **24**:257 (Oct.) 1940.

In 1912 Chavanne reported a case of asthma in a child aged 14 years which had existed for twelve years and which was relieved immediately by the removal of a papilloma of the uvula. In 1929 a second case was observed. The patient, aged 7½ years, had had monthly attacks of asthma since the age of 2 years. No abnormality was discovered except hypertrophied palatine tonsils. Complete relief was obtained by tonsillectomy.

In both cases the asthma reflex was of purely pharyngeal origin, without nasal relay or concomitant nasal lesion. The reflex in the first case was dependent on the pneumogastric nerve, and in the second the trigeminus nerve was responsible. The observations are important in indicating the possibility of a pharyngeal origin of asthma. Cases of this type are rare. The majority of cases of asthma belong in the realm of general medicine.

DENNIS, San Diego, Calif. [ARCH. OTOLARYNG.].

CAVERNOUS HEMANGIOMA OF THE LARYNX. ARISTIDES MONTEIRO, Acta med., Rio de Janeiro **6**:263 (Nov.) 1940.

The author reports a case of cavernous hemangioma of the larynx about the size of a bean which was expelled during a coughing spell. The disease apparently lasted about five years, and the tumor was found on the anterior commissure. Owing to the size and apparent interference with respiration, tracheotomy was considered, but during the examination the

patient began to cough forcibly and brought up the tumor mass. There was little bleeding. The cords returned to their normal appearance, and the patient was completely cured when examined a year later. Histologic examination revealed a cavernous hemangioma.

PERSKY, Philadelphia [ARCH. OTOLARYNG.].

CONGENITAL AUDITORY ATRESIA: ITS PLASTIC REPAIR WITH FUNCTIONAL RESTORATION OF HEARING AND PHONATION IN THE DEAF-MUTE. FELIX VEINTEMILLAS, Artistica, April 1940.

Veintemillas describes a method of plastic repair for congenital atresia of the ear in which he made a postauricular incision through the skin and retracted the tissue forward to expose the temporal bone in the region of the mastoid. Using either a trephine or a chisel, he made a funnel-shaped or cylindric canal into the more or less rudimentary middle ear. The canal had the promontory as its base. Then, utilizing the skin around this opening, he made a cutaneous flap extending into the new canal which insured both the preservation and the epidermal lining of the canal. The residual auricular or cartilaginous appendage was moved backward, sliding over the new-formed canal like a bridge, and was sutured in this position so that the canal was definitely anterior to the appendage and resembled a normal canal.

He found that deaf-mutes with this condition were successfully cured provided that the operation was performed at a suitable age. His best results were obtained in those between the ages of 5 and 12 years. Prior to the fifth year he encountered difficulty in obtaining satisfactory results. This was due to the incomplete development of the temporal bone and mastoid process, which afforded only a limited operative field. After the twelfth year the results again were not very favorable, owing to functional progressive atrophy of the acoustic nerves. His patients required reeducation so that they could learn speech in association with the recovery of the hearing. This necessitated prolonged conscientious education in speech. He reports on 8 patients in whom 12 reconstructions were made. His first patient, operated on in 1922, enjoyed a complete recovery of hearing and speech.

PERSKY, Philadelphia [ARCH. OTOLARYNG.].

POSTOPERATIVE HEMORRHAGES FROM THE TONSILS AND ADENOIDS. ANGEL BUSTILLOS and FRANZ C. JAHN, Bol. de los hosp. **38**:289 (June) 1939.

The authors discuss the etiologic factors that may predispose to post-tonsillectomy hemorrhages. They advise careful attention to prophylaxis and recommend that before operation patients be given calcium chloride supplemented by vitamin C. Liver extract, given both orally and parenterally, should also be used. They recommend that operation be postponed in the presence of certain conditions, namely, the residual period of an acute infection of the upper respiratory tract; menstruation; sudden changes in atmospheric conditions; active therapy, particularly the arsenic and bismuth treatment of syphilis; hemorrhagic diathesis, and secondary anemia.

If hemorrhage should occur, they recommend first the use of tampons saturated with one of the various coagulants. This is particularly valuable in the presence of bleeding from the adenoids. Here the postnasal pack should be inserted. In the tonsillar fossae ligation of the bleeding area is indicated. Transfusions, either autogenous or homogenous, are necessary in cases of the continuous or profuse type of hemorrhage.

PERSKY, Philadelphia [ARCH. OTOLARYNG.].

POSTANGINAL SEPSIS. ARTHUR WEDER, Pract. oto-rhino-laryng. **3**:193 (Oct.) 1940.

Weder presents a series of 30 cases of septicemia with complications following acute angina. There were 21 fatalities and 9 cures. He attempts to classify the anginas as local and systemic infections. Often there is no sharp line of demarcation at which one form merges into the other. The course may be one of a purely hematogenous or a lymphatic route; there may be an interstitial phlegmonous process, or there may be a combination of two or more avenues of extension.

The diagnosis depends on a history of local pain and difficulty in swallowing, elevated temperature and chills. There are leukocytosis, with a marked shift to the left in the Schilling count, a decrease or complete absence of eosinophils and bacteremia, which, however, is not always present.

The usual sequelae of the tonsillitis are peritonsillar abscess, a phlegmon in the parapharyngeal space and, eventually, thrombosis of the internal jugular vein. The thrombophlebitis carries with it the usual sequelae, such as metastasis both to the various vital organs

and to intracranial structures. The infection from the parapharyngeal space may spread to the parotid gland, the retropharyngeal space, the mediastinum or the endocranium.

Treatment in the cases of subacute infection is tonsillectomy, but this operative procedure has also been recommended in the presence both of acute tonsillitis and of a peritonsillar abscess. When the pathologic process has extended to the internal jugular vein, ligation of both this and the facial vein is recommended, together with evacuation of any suppurative collection, either peritonsillar or parapharyngeal. Removal of any infected cervical glands should be considered at the time the jugular vein is ligated.

Conservative treatment in cases of this condition has only a secondary role, particularly after the onset of septicemia or thrombosis of the jugular vein. Weder mentions the numerous chemotherapeutic measures employed, including the use of sulfanilamide and some of its derivatives. He stresses the urgency for surgical intervention, even though the tonsils show evidence of acute inflammation, and blames the high mortality rate on the fact that a great number of his patients were admitted to the hospital too late.

PERSKY, Philadelphia [ARCH. OTOLARYNG.].

Diseases of Lungs, Pleura and Mediastinum

LOEFFLER'S SYNDROME. ADELAIDO RIBEIRO, Pediat. e puericultura **9**:120 (June) 1940.

A brief historical résumé is made of the clinical and roentgen symptoms of Loeffler's syndrome, chiefly represented by pulmonary infiltrates, shadows, etc., and eosinophilia. The author states that no definite cause is known and that he believes the syndrome to be caused by various factors, such as parasitosis, typhoid, grip and measles.

He calls attention to the fact that Loeffler's syndrome may simulate a precocious tuberculous infiltrate and warns against the dangers, especially medicosocial, of not establishing a definite diagnosis in such a case.

A clinical case is presented. The patient was a 16 year old schoolboy, first seen with high fever and condensation shadows of the lungs, which appeared and disappeared about every four months. Eosinophilia was present. Investigation disclosed an opacity of the right maxillary sinus.

The author believes that the syndrome was caused in this instance by the sinus infection, which acted focally.

SOTO, Habana, Cuba.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

HEMORRHAGIC RECTOCOLITIS IN A GIRL OF TWELVE YEARS. ARMAND-DELILLE, ABRICOSSOFF and JOUSSEMET-LEFÉVRE, Bull. Soc. pédiat. de Paris **37**:556, 1940.

The girl's health was exceptionally good until the month of July 1939. The first intimation of illness was the passage of a stool with abundant fresh blood. From then to October 1939, such stools were of almost daily occurrence; the patient became anemic, thin and subfebrile, with five or six bloody stools a day in October. The entire abdomen was tender, especially in the left iliac fossa. All other examinations revealed no abnormalities. The blood picture showed 3,250,000 red cells and 10,500 leukocytes, 75 per cent of which were polymorphonuclear. Seroagglutination tests for the typhoid and dysentery groups gave negative results. The proctoscopic investigation revealed an inflamed mucosa of the entire rectal and sigmoidal areas. A generous and varied diet was offered, together with liver extract and small, repeated transfusions were given. In addition, liberal amounts of vitamin A and vitamin C were employed. Within three weeks, there was noticeable improvement; the patient had gained in weight and strength and the anemia was visibly corrected. There was slight bleeding, however, and after six weeks the patient was again hospitalized with the original clinical picture. Under the same management, there was little gain, and the girl was discharged Feb. 10, 1940, in a pitiable state. Death ensued some days later.

The advisability of direct rectal examination is urged, and attention is called to the extremely unfavorable prognosis.

AMESSE, Denver.

ACUTE HEMORRHAGIC PANCREATITIS IN A SIX YEAR OLD CHILD. M. R. ARANA and A. L. GARCIA, Arch. argent. de pediat. **13**:27 (Jan.) 1940.

Acute hemorrhagic pancreatitis is extremely rare in early childhood and must be always thought of when one is confronted with an acute abdominal condition in a child at any age.

The child showed many symptoms similar to those observed in adults, extremely severe epigastric pain coming on abruptly, followed by frequent and repeated vomiting. The vomitus was intensely bile stained, but there was no vomiting of fecal matter.

The symptoms in this child differed from those in adults in that there was no intense shock simulating collapse and no marked degree of cyanosis, but there were hypothermia, cold extremities, frequent and thready pulse and great restlessness. The abdominal pain was more severe on the left side than on the right side of the midline, and the muscular spasm was also more pronounced on the right side. Ecchymotic spots appeared on the abdominal wall. Wohlgemuth's test for diastase in the urine gave a positive reaction, and there was hyperglycemia.

The authors resorted to surgical intervention with simple drainage followed by medical treatment. This consisted in giving a diet which made the least demand on pancreatic secretion. Dextrose solution combined with insulin, administered by subcutaneous and intravenous routes, and cardiovascular stimulants were given as needed. Atropine and morphine were used to diminish the pancreatic secretion and ease the pain.

The authors pointed out that there is considerable division of opinion as to the desirability of early operation for this condition. Sometimes it is well to use medical treatment first and then have recourse to surgical intervention later.

SCHLUTZ, Chicago.

Nervous Diseases

OBSTETRIC PARALYSIS INVOLVING UPPER AND LOWER LIMBS. LANCE, Bull. Soc. pédiat. de Paris **37**:512, 1940.

At the age of 10 weeks, an infant was brought to the hospital with paralysis of both arms. The birth history was without incident, and there had been no obstetric trauma. The patient presented the characteristic features: internal adduction-rotation of the arm with exaggerated pronation of the forearm. For a few days the arms were almost entirely immobile, but little by little normal motion was regained, especially on the left. Roentgenograms showed no epiphysial separation.

The mother called attention to the fact that since birth the infant had shown no movement in the lower limbs. Examination revealed that motion could be obtained by pricking with a needle, but in a much less degree than the normal response. The complete picture, as proved by electrical reactions, was that of paralysis more or less severe in all four limbs.

AMESSE, Denver.

CHANGES IN THE SPINAL CORD IN LANDRY'S PARALYSIS. E. MOSIG, Ztschr. f. d. ges. Neurol. u. Psychiat. **170**:331 (Sept.) 1940.

Mosig reports 4 cases of Landry's paralysis, with studies of the spinal cord and nerve roots. Two of the patients were males and 2 females. The ages varied from 1 to 58 years. The duration of the illness was up to ten days. The clinical picture in each case was that of ascending paralysis. In none of the cases was there any evidence of inflammatory disease in the spinal cord. In fact, no significant alterations were noted in any of the structures of the cord. The ganglion cells were intact. There were severe changes in the nerve roots, especially the anterior. These lesions were apparently degenerative, involving especially the axis-cylinders. There were less striking alterations in the myelin sheaths.

SAVITSKY, New York [ARCH. NEUROL. & PSYCHIAT.].

Diseases of the Genitourinary Tract

TREATMENT OF ENURESIS BY MEANS OF INJECTIONS OF ANTERIOR PITUITARY EXTRACTS. ALVARO BAHÍA and JOSÉ PEROBA, Pediat. e puericultura **8**:58 (March) 1939.

The authors report the use of anterior pituitary extracts in cases of urinary incontinence, with results sufficiently gratifying to recommend it. They have followed the method proposed by Georges Cain, but the technic was changed, inasmuch as the substance was given parenterally (intramuscular injections) rather than orally, much smaller doses being required in this way.

The dosage employed was: for children 2 to 4 years old, 50 rat units on alternate days; for children of school age, 100 rat units on alternate days. The authors report that only rarely was a repeat series of injections required and that when such was the case these were given after an eight-day interval from the first.

In a series of 16 cases studied, the percentage of definite cures was greater than 50, which is considerably more satisfactory than that found with previous methods.

SOTO, Habana, Cuba.

Diseases of the Ductless Glands; Endocrinology

LEVULOSURIC DIABETES. PAISSEAU and BUCHMANN, Bull. Soc. pédiat. de Paris **37**:613, 1940.

Pure levulosuria, independent of a clinical syndrome associated with the metabolism of other carbohydrates, is extremely rare. To establish such a diagnosis it is essential that the polarimetric reactions should be considered as well as the Sélivanoff reaction and the identification of osazone. A review of the literature reveals but 25 reported cases in addition to the present case, the third reported from France. The disease is apparently uncommon in childhood. The authors discuss in full an instance of levulosuric diabetes in a boy of 11 years who entered the hospital Feb 14, 1939 because of insomnia and extreme agitation. The history showed that sugar had been found in the urine four years before, and monthly examinations since that time had always indicated the presence of sugar, the amount varying from 1 to 3 Gm. per liter with a carbohydrate-free diet to 5 to 11 Gm. per liter with a diet containing sugar. Examination showed an extremely nervous subject with the usual defects of dentition characteristic of hereditary syphilis. The fasting index for urinary sugar was 1.05 Gm. per liter; there was deviation to the left on polarimetric study, with a positive Sélivanoff reaction. There was total absence of hyperglycemia. Sulfarsphenamine was administered in the proper dosage for the patient's weight, and the levulosuria promptly disappeared. Examinations six months later indicated entirely normal conditions.

AMESSE, Denver.

ADDISON'S DISEASE, VITILIGO, CREATINMETABOLISM. J. SCHARFF, Arch. f. Kinderh. **118**:97 (Oct. 27) 1939.

Scharff reports on a case of Addison's disease and vitiligo in a girl of 12 years. There was an increase of creatine in the urine corresponding to the decrease in muscular strength. Physical exercise, such as climbing stairs and gymnastics, performed almost to the limit of endurance caused a remarkable decrease in the excretion of creatine.

ARON, Chicago.

Diseases of the Muscles, Bones, Joints and Lymph Glands

COSTOVERTEBRAL RETICULOSARCOMA OF EWING IN AN INFANT OF SEVEN MONTHS. M. J. MÉZARD, Bull. Soc. pédiat. de Paris **37**:551, 1940.

The patient, first seen on Aug. 29, 1936, was a 7 month old girl apparently normal in all respects at birth, breast fed for three months and with average development during that period. One month before admission to the clinic, the baby suffered from nasopharyngeal catarrh followed by otitis media on the right side. A few days later it was noted that the patient had lost all motion of the lower limbs. Examination showed a well nourished, vigorous infant without signs of rickets or anemia. The only positive evidence of disease were subacute rhinopharyngitis with an abundant purulent secretion and spastic paraplegia showing the customary syndrome. Percussion of the lower vertebrae elicited a sharp cry of pain; the right costovertebral angle seemed more rigid than the left. Roentgenograms revealed a triangular, opaque shadow embracing the right half of the four lower dorsal vertebrae, which in this area appeared twice their normal width. The cutaneous reaction to tuberculin was negative. It was considered probable at this time that the patient was suffering from osteomyelitic abscess of the vertebrae, secondary to the rhinopharyngeal infection. Two months later there were external evidences of a tumor over the last two dorsal vertebrae, a hard nonfluctuating mass about the size of a walnut. A dorsal puncture withdrew a bloody fluid, in which there were in addition to red cells polymorphonuclear neutrophils and large elements identified as reticulocytes. Osteosarcoma was consequently ruled out, and a diagnosis of reticulosarcoma (Ewing) was made. Under intensive radiotherapy the process appeared localized, and the patient when examined nearly three years later seemed in good health with the exception of paraplegia. The advantages of early puncture of such tumors are stressed.

AMESSE, Denver.

PRESTERNAL STAPHYLOCOCCIC ABSCESS COMPLICATING OSTEOMYELITIS. ARMAND-DELILLE, LASCOMBE and GYVIN, Bull. Soc. pédiat. de Paris **37**:580, 1940.

A rare invasion is reported in a boy of 10 years, a refugee from the war area near Paris. This patient complained of severe thoracic pain during an acute febrile attack, and the con-

dition was tentatively diagnosed as pneumonia. Several days later a presternal tumefaction was observed, and at the time of examination by the authors there was a fluctuating abscess as large as an egg. The temperature was 38.2 C. (100.8 F.). There were no evidences of pneumonia. The authors at first suspected a cold abscess; a tuberculin cutaneous test was ordered, and this elicited a negative reaction. On puncture and later on incision, large quantities of pus containing staphylococci in pure culture was obtained. The boy recovered, but a small fistula was left.

AMESSE, Denver.

SYNDROME OF BLUE SCLERA: ITS PRESENCE IN FIVE GENERATIONS. F. CHIMANI, Monatschr. f. Ohrenh. **74**:548 (Nov.) 1940.

The observations on a girl aged 18 evidencing all signs of the syndrome of blue sclera, namely, fragility of the bones and deafness of an otosclerotic type, made possible the study of her family tree. The patient had had several fractures; so had her twin sister and her mother. All of them had blue scleras, but the twin sister showed only slight impairment of hearing. The mother evidenced serious loss of hearing, which had increased with each succeeding pregnancy. A fourth symptom purportedly belonging to this syndrome, a special configuration of the skull, could not be observed. "Rheumatic" pains in the joints in cases of this condition are explained by the traumatic influence on the joints.

From his study of the family tree, shown in graphic form, and from a survey of the available literature, Chimani concludes that the syndrome of blue sclera is predominantly inherited, both sexes being subject to it and both passing it on alike. Only manifest carriers are capable of transmitting the condition to their offspring. He mentions several theories as to its origin, such as avitaminosis, syphilis and hypofunction of the parathyroid glands. In his opinion, the entity should be placed in the category of a congenital (inheritable) deficiency of the mesenchyme. He further ventures the opinion that otosclerosis, being associated with this syndrome, might be not altogether a disease per se but a part of this systemic disturbance. This is especially evident in some family trees in which the otosclerotic component of the syndrome has become predominant.

LEDERER, Chicago [ARCH. OTOLARYNG.].

Diseases of the Eye

SURGICAL TREATMENT OF FUNCTIONAL STRABISMUS. J. SVERDLICK, Arch. de oftal. de Buenos Aires **15**:246 (May) 1940.

The author attributes the actual perfection of the surgical treatment of functional strabismus to the improvement in knowledge of neuromyology. The operations per se, as well as the preorthoptic treatment and the following orthoptic training, only constitute stages in the sensorimotor coordinative treatment of strabismus, a combination leading to the attainment of the full benefit to the patient by a realization of the therapeutic equation cosmetic result plus reestablishment of binocular vision.

Surgical intervention is indicated when preorthoptic treatment and orthoptic training have failed to correct the deviation or other factors, such as a psychic handicap and economic difficulties.

Sverdlick reduces the various operative technics to those of lengthening the muscle by (*a*) tenotomy or (*b*) recession and those of shortening the muscle by (*a*) advancement with or without resection and (*b*) tucking.

Simple tenotomy owes its popularity to its extreme facility, which is more than counterbalanced by its multiple disadvantages from lack of accuracy and poor cosmetic results. After mentioning the general objectives, requirements and technic of the other procedures, the author takes up the question of the most appropriate age for operation. He is opposed to all operations before the age of 6 years, preferring the age from 8 to 10. Prior to this period, preorthoptic treatment and orthoptic training conducive to the prevention of amblyopia, loss of central fixation and development of an anomalous retinal correspondence should be carried out.

The choice of the operative procedure should be subordinated to the physiopathologic conditions present and to a study of the patient's visual function, recession being indicated when there is an excess of divergence or an excess of convergence with hyperkinesis of the internal rectus muscle and advancement when there is a lack of divergence or an insufficiency of convergence with hypokinesis of the internal or the external rectus muscle. The results depend not only on the method chosen but on the ability of the surgeon. The author prefers operating by successive stages.

C. E. FINLAY [ARCH. OPHTH.].

COMPARATIVE STUDIES ON "PHACOMAS" OF THE EYEBALL AND ITS ADNEXA: REPORT OF CASES. C. PASCHEFF, Klin. Monatsbl. f. Augenh. **104**:595 (May) 1940.

Congenital spots occur on the eyes which are similar in development to nevi of the lids and conjunctiva but which contain no nevus cells. Pascheff accepts Van der Hoeve's term *Phakoma* (phacoma). He classifies the spots into four groups: (1) phacoma palpebrae, to which belong naevus flammeus, infantile glaucoma, neurofibroma plexiforme palpebrae with infantile glaucoma, elephantiasis neurofibromatosa palpebrae and congenital posterior cortical cataract; (2) phacoma iridis and glaucoma simplex; (3) phacoma retinae, with the subdivisions phacoma retinae of Recklinghausen's disease and phacoma iridis of Bourneville's disease, and (4) phacoma nervi optici, including primary tumor of the optic nerve, which is rare, and angiofibromatous or pigmented meningoblastoma of the optic nerve. The various types are illustrated with about twenty-five photographs, some of them photomicrographs.

The author concludes that these tumors are not malign but are apt to cause changes in the adjoining bones and damage to vision. The tumors may be classified, according to their location, as phacomas of the lids, iris, retina and optic nerve. Phacomas of the lids (neurofibroma and naevus flammeus) may be accompanied by infantile glaucoma, astigmatism, cataract and amblyopia. There are congenital forms, such as phacoblastoma. Phacomas of the iris are usually combined with glaucoma, according to Pascheff's observation.

Phacomas of the retina are rare and are coupled with phacomas of the skin (Recklinghausen's, Bourneville's and Sturge-Weber's disease). Phacomas of the optic nerve are very rare; Pascheff observed only 2 cases in forty years. Primary congenital tumors of the optic nerve occur which do not originate from Schwann's sheaths of the optic nerve, as they are absent in the fibers of the optic nerve. The two forms of tumors of this nerve, previously mentioned, may cause choked disk through adhesions to the optic nerve, or they may proliferate far into the orbit, leading to amaurosis. Amaurosis occurred in 1 of Pascheff's cases; no recurrence or cerebral lesion developed during eight years of postoperative observation.

K. L. STOLL [ARCH. OPHTH.].

Skin Diseases; Allergy

PHYSICAL DIAGNOSIS OF EDEMA IN INFANCY. LUIZ TORRES BARBOSA, Arch. de pediat. **11**:1357 (Sept.) 1939.

This is a most exhaustive study of the etiology, pathogenesis and physical diagnosis, including prognosis, of edema in infants. The whole work, which is well presented and profusely illustrated, is divided into three parts, as follows:

I. Physiologic Peculiarities of Water Metabolism in Infants

II. Principal Diagnostic Resources (including a discussion of the tests employed)

III. Clinical Study of the Edemas

1. General Discussion
2. Different Clinical Forms:
   - In the newborn
   - In nutritional disturbances of infants
   - In circulatory disorders
   - In nephropathies
   - In hepatopathies
   - In helminthiasis
   - In infections and cachexias
   - In endocrine, anaphylactic and nervous disturbances
3. Diagnostic Orientation

The author concludes that even though in general a discrimination may be made between renal and extrarenal edema this difference is never absolute, much less definitive. He stresses the fact that edema in an infant is always serious.

SOTO, Habana, Cuba.

Book Reviews

The Biological Action of the Vitamins: A Symposium. Edited by E. A. Evans Jr., Associate Professor of Biochemistry, The University of Chicago. Price, $3. Pp. 227, with 45 illustrations. Chicago: University of Chicago Press, 1942.

This collection of papers is concerned with the vitamins of the B complex, including biotin and choline, vitamin K and the economy of phosphorus in the animal organism. The introductory chapter, presented by C. A. Elvehjem, reviews the growth of knowledge of the action of the vitamins with special reference to their relation to enzyme systems and to bacterial growth. This phase is covered in more detail in the specific chapters on the various vitamins. Methods and results of animal experimentation are given, and wherever possible the relationship to human nutrition is shown. The discussions are exceedingly stimulating from the point of view both of how knowledge of these vitamins and of the phosphorus economy has grown and of how much remains to be found out.

Contributors are C. A. Elvehjem, S. Ochoa, Norman Jolliffe, Paul György, W. H. Sebrell, David T. Smith, S. Lepkovsky, Roger J. Williams, Edgar S. Gordon, Vincent du Vigneaud, Wendall H. Griffith, Franklin C. McLean, D. W. MacCorquodale, H. P. Smith and E. D. Warner. The occasion of the papers was a joint symposium in connection with the fiftieth anniversary celebration of the University of Chicago. An accompanying volume on respiratory enzymes has also been published. Unfortunately no index has been compiled.

Methods for the Study of Personality in Young Children. Monograph of the Society for Research in Child Development of the National Research Council. Edited by Eugene Lerner and Lois Barclay Murphy. Price, $2.00. Pp. 289, with 44 illustrations. Washington, D. C.: The National Research Council, 1941.

This monograph describes in detail numerous methods for determining objectively by specific tests the personality responses of nursery school and kindergarten children. The writers and observers are all trained in progressive education.

The monograph is divided into four parts as follows: experiments in free play, experiments in group play and readiness for destruction, experiments in active play technics, observing children in nursery school situations.

Studies of this kind are extremely valuable, because they promote an objective attitude toward children, give valuable information about growth and focus the attention of physicians, teachers and parents on fascinating growth patterns rather than on the forcing of impossible standards on children. From studies such as these one will be able to understand the individual personality characteristics of children in the same way that one now recognizes individual intelligence characteristics. It will then be possible to help each child reach a maximum growth.

Mental Illness: A Guide for the Family. By Edith M. Stern with the collaboration of Dr. Samuel W. Hamilton. Price, $1.00. Pp. 134, with no illustrations. New York. The Commonwealth Fund, 1942.

The purpose of this book is to point out to the laity, and especially to the other members of a family in which there is a mentally ill member, the present scientific conception of the illness. Mental illness is pictured as no different from any other type of illness; its hereditary factors are given proper importance, and the error of feeling disgrace and shame is emphasized. There is a discussion of mental hospitals and their place in a medical system. This book should be read by all persons who have to deal with the relatives of mentally sick people and can be recommended to the families themselves.

Civilian Health in Wartime. By Dr. Francis R. Dieuaide. Price, $2.50. Pp. 328, with no illustrations. Cambridge, Mass.: Harvard University Press, 1942.

The author has provided for the nonprofessional reader a general picture of some of the health problems which have always existed in this country but which have been made more conspicuous by the war effort. Problems of the general population and of some special groups are considered. Special attention is given to nutrition, infectious diseases, mental health and morale. References are offered the reader who is interested in obtaining further and more specific information concerning various phases of the subject.

The Principles and Practice of Medicine. By the late Sir William Osler, Bart., M.D. Edited and revised by Henry A. Christian, A.M.A., M.D., LL.D., Hon. Sc.D., F.A.C.P. Price, $9.50. Pp. 1,474, with 9 illustrations. New York: D. Appleton-Century Company, Inc., 1942.

The fourteenth edition of Osler's Principles and Practice of Medicine, edited by Henry A. Christian, justly commemorates fifty years of a living, vital textbook. In preparing this book the editor, losing none of the charm of the original text so brilliantly conceived and presented by Dr. Osler, has added to the preceding editions to a degree that justifies this semicentennial edition. The general method of presenting the text remains essentially the same, although any one familiar with the previous editions will probably find this one as readable and delightful. Through the careful and thoughtful editorship of a thoroughly trained clinician recent advances in diagnosis and therapy have been added.

A few features deserving especial commendation reveal both the teacher and the practitioner in the editor. He introduces the text by a brief and thought-provoking discussion of psychosomatic medicine and follows with a chapter on functional diseases of the nervous system. By so doing he has placed emphasis on a phase of medicine which has been too frequently neglected by the medical practitioner and in which the medical school curriculum has been notoriously remiss.

Another practical addition is the up-to-date and well chosen bibliography at the end of each chapter. These references supplement the necessarily concise and at times limited discussions inherent in a book of this type. They are of particular value to the student who is in need of this ready reference for outside reading.

Dr. Christian is to be complimented on his rearrangement of and additions to the text without loss of the "spirit of the past editions, which has seemed to fill so well the needs of students and practitioners."

This book should be in the library of every physician, whatever his specialty, and may well be used as a text for medical students.

Las vitaminas en la alimentación del lactante. By Enrico Jaso. Price, none given. Pp. 224, with 23 illustrations. Barcelona: Editorial Cientifico Medica, 1942.

The first part of the book contains a description of the various vitamins and illustrations of the effects of their deficiency on laboratory animals. This is followed by a discussion of the role of vitamins in antepartum care, their influence, their content in human and in animal milk and their metabolism. This is a complete and interesting little book, written in Spanish. It is up to date and contains a bibliography of 253 authors.

News and Comment

GENERAL NEWS

Subcommittee on Maternity and Child Care.—Dr. Thomas Parran, Chairman of the Committee on Public Health and Medical Care of the Office of Foreign Relief, has named the following Subcommittee on Maternity and Child Care: Drs. Martha Eliot (chairman), Nicholson J. Eastman, Clifford G. Grulee, Henry F. Helmholz, Edwards A. Park and Joseph Stokes.